# Intravenous Acetaminophen Improves Outcomes After Transapical Transcatheter Aortic Valve Replacement

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**Objective:** Complications with opioid-based postoperative pain management have led to guideline recommendations for a multimodal analgesia strategy incorporating nonopioid agents. We evaluated the opioid-sparing effect of intravenous acetaminophen in patients undergoing transapical transcatheter aortic valve replacement.

**Methods:** A multimodal pain management strategy that incorporated intravenous acetaminophen was retrospectively evaluated in 43 patients undergoing transapical transcatheter aortic valve replacement between November 2012 and March 2014. Before intravenous acetaminophen formulary availability, 23 patients received standard postoperative pain management interventions including intravenous narcotics and oral narcotics/acetaminophen. After intravenous acetaminophen availability, 20 patients received intravenous acetaminophen (4 g/d, ≥4 doses) and supplemental intravenous and nonacetaminophen oral narcotics. Daily narcotic dose (standardized to morphine equivalents), drug cost, and hospital length of stay were compared between groups.

**Results:** Baseline characteristics were similar between intravenous acetaminophen (n = 20) and nonintravenous acetaminophen (n = 23) patients including the Society of Thoracic Surgery mortality risk (10.5% vs 9.0%, $P = 0.3$). The median number of intravenous acetaminophen doses was 6.5 (interquartile range = 4.0–18.5), with a median cost per patient of US $221 (interquartile range = $136–$629). Patients who received intravenous acetaminophen used significantly fewer morphine equivalents on postoperative day 0 compared with patients not receiving intravenous acetaminophen (22.5 vs 45.0 morphine equivalents, $P = 0.03$) and had a shorter median length of stay (5.0 vs 7.0 days, $P = 0.007$). After adjusting for the Society of Thoracic Surgery risk, intravenous acetaminophen continued to be associated with a reduction in median postoperative length of stay [−1.9 days (95% confidence interval = −0.9 to −8.2 days), $P = 0.049$].

**Conclusions:** In patients undergoing transapical transcatheter aortic valve replacement, a multimodal pain management strategy incorporating intravenous acetaminophen was associated with reductions in narcotic use on the day of surgery and overall length of stay.

**Key Words:** Intravenous acetaminophen, Transapical transcatheter aortic valve replacement, Multimodal analgesia, Clinical outcomes, Elderly.

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Oral and intravenous (IV) opioid agonists traditionally have been important analgesics for the treatment of pain in the immediate postoperative setting.[1–3] In the United States, up to 99% of patients who undergo major surgery are treated with an opioid analgesic.[4] However, overreliance on opioid monotherapy in the inpatient setting raises potential health risks for patients, particularly in the form of adverse drug events (ADEs), including postoperative nausea and vomiting, pruritus, sedation, delirium/confusion, urinary retention, constipation and ileus, and respiratory depression.[5,6] These opioid-related ADEs can contribute to patient discomfort and dissatisfaction, delayed recovery from surgery, increased hospital length of stay (LOS), and increased healthcare costs.[7,8]

Numerous surgical and nonsurgical medical societies and accrediting and quality organization guidelines recommend the use of multimodal analgesia (MMA) to reduce exposure to opioids.[2,6,9–14] Many also recommend scheduled use of nonopioid analgesics [eg, acetaminophen (known outside the United States as paracetamol), cyclooxygenase-2 inhibitors, or nonsteroidal anti-inflammatory drugs] as the first-line foundation of MMA. Unfortunately, contraindications to the use of some nonopioid agents such as cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory drugs, particularly in elderly patients undergoing cardiac surgery, have limited implementation of these recommendations.

In the current study of a homogenous elderly population, we assessed clinical outcomes including daily opioid requirements and hospital LOS in patients undergoing transcatheter aortic valve replacement using a transapical approach (TA-TAVR) who received opioids without IV acetaminophen (IVA) or an MMA regimen including IVA.

## METHODS

The Saint Luke's Mid America Heart Institute's Transcatheter Valve Therapy database was queried for consecutive patients undergoing TA-TAVR between November 2012 and March 2014. Consecutive patients who underwent surgery before formulary approval of IVA received IV and acetaminophen-containing

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oral opioids for postoperative pain management. Those who underwent surgery after formulary approval of IVA received IVA (administered as 1 gram at induction of anesthesia and every 6 hours after surgery) plus IV and nonacetaminophen oral opioids for postoperative pain management. Patients were excluded from this analysis if they remained intubated for longer than 48 hours and/or died during the index hospitalization. An additional retrospective electronic medical record review was conducted to assess clinical outcomes and individual postoperative pain management regimens. All postoperative opioid doses were standardized to morphine equivalents (MEs) using an algorithm from the Centers for Disease Control and Prevention.[15] The cost of IVA was assessed as US $34.50 per dose.

Descriptive statistics for continuous variables included frequency counts, median, minimum, maximum, and interquartile range. Frequency and percentages were calculated for categorical variables. Continuous variables were compared using the *t* test, and a median regression model was used to adjust for the Society of Thoracic Surgery (STS) risk when comparing hospital LOS. All statistical significance testing was two-tailed using $\alpha = 0.05$. Data summary and analyses were performed with SAS® 9.2 (SAS Institute Inc, Cary, NC USA).

## RESULTS

A total of 45 patients underwent TA-TAVR between November 2012 and March 2014 at Saint Luke's Mid America Heart Institute. Before formulary availability of IVA, 24 consecutive patients received IV narcotics and oral acetaminophen-containing opioids for postoperative pain management. After IVA became available, 21 consecutive patients received MMA consisting of scheduled IVA with IV narcotics and oral nonacetaminophen opioids for breakthrough pain. Two patients, 1 from each group, remained intubated for longer than 48 hours, died during the index hospitalization, and were excluded from further analysis. Demographics and baseline characteristics (Table 1) were similar between IVA (n = 20) and non-IVA (n = 23) TA-TAVR patients including the STS mortality risk (10.5% vs 9.0%, $P = 0.3$). The median number of IVA doses was 6.5 (interquartile range = 4.0–18.5), with a median cost per patient of US $221 (interquartile range = US $136–$629).

Table 2 summarizes daily MEs. Opioid use is displayed through postoperative day (POD) 2 (Fig. 1) because the median duration of IVA use was 1.5 days (6.5 doses). Patients who received IVA received significantly fewer MEs on POD 0 than non-IVA patients (median = 22.5 mg vs 45.0 mg, $P = 0.03$), and there was a trend toward reduced overall opioid consumption through POD 2 (median ME = 66.9 mg vs 90.0 mg, $P = 0.10$).

The median LOS was lower for patients who received IVA than for those who did not receive IVA (5.0 vs 7.0 days, $P = 0.007$). After adjusting for the STS risk using a median regression model, the use of IVA remained associated with

**TABLE 1.** The TA-TAVR Patient Demographics and Baseline Characteristics by Postoperative Analgesic Treatment

| | Total (n = 43) | Intravenous Acetaminophen (n = 20) | No Intravenous Acetaminophen (n = 23) | *P* |
|---|---|---|---|---|
| STS risk score, mean (range) | 9.0 (7.0–12.0) | 10.5 (7.0–13.9) | 9.0 (7.0–10.0) | 0.312 |
| Age, mean (range) | 86.0 (81.0–89.0) | 86.0 (83.0–88.5) | 85.0 (80.0–89.0) | 0.296 |
| Sex, n (%) | | | | 0.474 |
| Female | 24 (55.8) | 10 (50.0) | 14 (60.9) | |
| Male | 19 (44.2) | 10 (50.0) | 9 (39.1) | |
| Previous CABG, n (%) | 19 (44.2) | 9 (45.0) | 10 (43.5) | 0.869 |
| Cardiovascular disease, n (%) | 15 (34.9) | 8 (40.0) | 7 (30.4) | 0.648 |
| Peripheral artery disease, n (%) | 20 (46.5) | 11 (55.0) | 9 (39.1) | 0.421 |
| Smoker, n (%) | 8 (18.6) | 4 (20.0) | 4 (17.4) | 1.000 |
| Hypertension, n (%) | 29 (67.4) | 17 (85.0) | 12 (52.2) | 0.065 |
| Diabetes, n (%) | 14 (32.6) | 8 (40.0) | 6 (26.1) | 0.431 |
| Lung disease, n (%) | | | | 0.531 |
| Mild | 6 (14.0) | 2 (10.0) | 4 (17.4) | |
| Moderate | 7 (16.3) | 3 (15.0) | 4 (17.4) | |
| None | 20 (46.5) | 12 (60.0) | 8 (34.8) | |
| Severe | 6 (14.0) | 2 (10.0) | 5 (21.7) | |
| Immunosuppressed, n (%) | 10 (23.3) | 4 (20.0) | 6 (26.1) | 0.716 |
| Preoperative NYHA class, n (%) | | | | 0.810 |
| 2 | 5 (11.6) | 3 (15.0) | 2 (8.7) | |
| 3 | 10 (23.3) | 4 (20.0) | 6 (26.1) | |
| 4 | 24 (55.8) | 12 (60.0) | 12 (52.2) | |
| Atrial fibrillation/flutter, n (%) | 8 (18.6) | 6 (30.0) | 2 (8.7) | 0.127 |
| Preoperative hemoglobin, mean (range) | 11.8 (10.6–13.0) | 11.4 (10.5–12.3) | 12.1 (10.9–13.4) | 0.377 |
| Preoperative creatinine, mean (range) | 1.4 (0.8–1.8) | 11.4 (0.9–1.8) | 1.3 (0.8–1.8) | 0.875 |
| Ejection fraction, mean (range) | 60.0 (45.0–60.0) | 60.0 (45.0–60.0) | 60.0 (47.5–60.0) | 0.905 |

CABG, coronary artery bypass graft; NYHA, New York Heart Association; STS, Society for Thoracic Surgery; TA-TAVR, transapical transcatheter aortic valve replacement.

**TABLE 2.** Median (Interquartile Range) LOS and Median (Interquartile Range) Morphine Equivalents by POD (0–4) in TA-TAVR Patients With and Without Intravenous Acetaminophen

| | Total | Intravenous Acetaminophen | No Intravenous Acetaminophen | |
|---|---|---|---|---|
| | n = 43 | n = 20 | n = 23 | *P* |
| LOS | 7.0 (5.0–9.0) | 5.0 (4.0–7.0) | 7.0 (6.0–16.0) | 0.007 |
| Opioid use (morphine equivalents) | | | | |
| Day 0 | 40.0 (20.0–60.0) | 22.5 (10.0–54.8) | 45.0 (30.0–60.0) | 0.033 |
| Day 1 | 27.5 (20.0–45.0) | 23.8 (20.0–45.0) | 30.0 (15.0–47.5) | 0.643 |
| Day 2 | 15.0 (7.5–30.0) | 12.5 (3.8–22.5) | 21.3 (7.5–42.5) | 0.239 |
| Day 3 | 7.5 (0.0–17.5) | 7.5 (0.0–15.0) | 7.5 (0.0–20.0) | 0.717 |
| Day 4 | 8.8 (0.0–22.5) | 0.0 (0.0–22.5) | 11.3 (0.0–37.5) | 0.389 |
| Total 4 days + day 0 | 92.5 (75.0–170.0) | 91.3 (55.0–119.8) | 135.5 (80.0–192.2) | 0.192 |
| Median (interquartile range) no. doses | 6.5 (4.0–18.5) | 6.5 (4.0–18.5) | | |

LOS, length of stay; POD, postoperative day; TA-TAVR, transapical transcatheter aortic valve replacement.

a reduction in median postoperative LOS [difference, −1.9 days (95% confidence interval = −0.9 to −8.2 days), $P = 0.049$].

## DISCUSSION

Opioid use continues to play an important role in the treatment of postoperative pain but has a well-documented association with adverse patient outcomes. Numerous efforts are under way, particularly among government agencies[16,17] and medical associations,[18] to curtail the use of opioids. Increased public demand for a high quality of care, a federal focus on value-based care,[19,20] and increased scrutiny by hospital accreditation agencies[6] are requiring hospitals to implement MMA strategies for the benefit of their surgical patients.

In our analysis, we found that incorporating IVA in an MMA pain management regimen for patients undergoing TA-TAVR was associated with a shorter hospital LOS and less opioid use on the day of surgery. Although the use of nonfemoral access to perform TAVR has dramatically decreased during the last 10 years with the advent of smaller devices and novel sheaths, the emerging field of transcatheter mitral valve replacement may spark a resurgence in transapical approaches, making an understanding of IVA in that scenario very helpful.

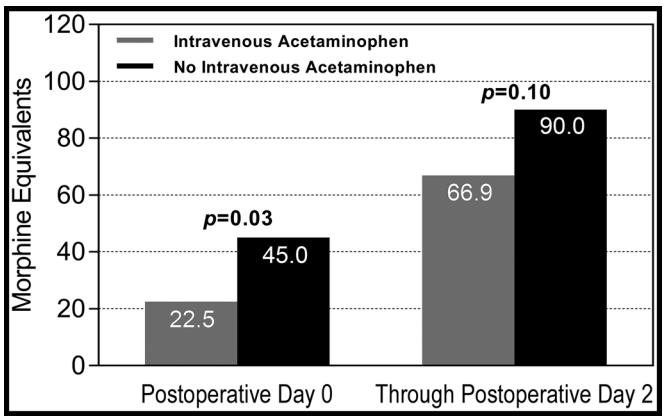


**FIGURE 1.** Opioid use in MEs (median) on POD 0 through POD 2 by postoperative analgesic treatment in TA-TAVR patients. ME, morphine equivalents; POD, postoperative day; TA-TAVR, transapical transcatheter aortic valve replacement.

The results from our analysis reinforce findings from randomized controlled trials demonstrating that the incorporation of IVA in an MMA regimen to treat postoperative pain can reduce LOS[21,22] and opioid analgesic use[23–25] for a broad range of surgical procedures. Findings from a prospective, double-blind, placebo-controlled trial of 60 adults undergoing cardiac procedures involving cardiopulmonary bypass demonstrated a strong trend toward a shorter hospital LOS for patients who received IVA (1 g every 6 hours for 4 doses) than for patients who received placebo ($P = 0.07$).[26] The shorter LOS was attributed to reductions in overall opioid consumption and therefore opioid-related adverse events when IVA was used in an MMA regimen. Additional randomized controlled trials evaluating IVA use for patients undergoing cardiac surgery have demonstrated a significant reduction in total opioid consumption[27] and a 21% reduction in the use of rescue opioids to treat acute pain.[28]

The use of MMA regimens has reduced opioid-related ADEs, LOS, readmissions, and costs across numerous surgical populations.[29–31] Shaffer et al.[32] conducted a study to estimate the effect of incorporating IVA in an MMA for postoperative pain management across numerous surgery types including cardiovascular surgeries. Their data from more than 2 million patient encounters (IVA used in 12.1%) across 297 hospitals showed that a reduction in opioid use by 1 level (ie, high to medium, medium to low, or low to none) was associated with a reduction in LOS of 18.5% (range = 10.7%–32.0%) and a total LOS-related cost savings of US $4.5 million (even after incorporating the cost of IVA). For patients undergoing cardiovascular surgery, the calculated LOS reduction for dropping 1 level of opioid use and adding IVA was 1.01 days (reduction from 4.01 to 3.00 days, −25.2%), leading to an estimated cost savings of US $660,000 per year for a medium-sized program.[32]

Unlike opioids, with known safety complications, IVA has not been associated with serious adverse reactions when used appropriately, including in patients undergoing major cardiac procedures. In a double-blind, placebo-controlled trial of 113 patients undergoing cardiac operations with a standard midline sternotomy, with harvesting of saphenous vein and internal thoracic artery, if indicated, patients received 12 doses of study drug (IVA 1 g or placebo) at 6-hour intervals (ie, for 72 hours), in addition to tramadol continuous infusion. Cardiorespiratory

 

parameters ($Pao_2$ and systolic arterial pressure) were similar between the two treatment groups through 72 hours, although patients in the placebo group had a significantly higher respiratory rate and heart rate 12 hours after surgery. Postoperative nausea and vomiting were noted in only three patients (6%) in the IVA group and one patient (2%) in the placebo group. No serious or significant adverse events were noted in either treatment group.[33]

Understanding the pharmacokinetics of acetaminophen is important to appreciate how the route of administration can affect pain control, particularly because IVA is more expensive then oral acetaminophen. Acetaminophen has a centrally mediated effect on pain and requires sufficient peak plasma concentrations to cross the blood-brain barrier and achieve adequate cerebrospinal fluid (CSF) concentrations. Compared with orally and rectally administered acetaminophen, IVA produces mean plasma concentrations that are 76% ($P = 0.0004$) and 256% ($P < 0.0001$) higher, respectively.[34] Intravenous acetaminophen results in therapeutic CSF levels within 15 minutes of administration and mean CSF concentrations that are 75% higher ($P = 0.0099$) than those of orally administered acetaminophen and 142% higher ($P = 0.0004$) than those of rectal acetaminophen.[34]

Even with appropriate oral dosing of acetaminophen in the postoperative period, failure to achieve adequate peak plasma concentrations with subsequent therapeutic CSF levels is further exacerbated by compromised gastric function in the postoperative setting.[35,36] Gastric dysmotility and subsequent reduced intestinal absorption of drugs are inherent issues in postoperative cardiac surgery patients, particularly those who are elderly patients, and concomitant administration of IV opioid analgesics further compounds these problems.[37] Although the current study did not specifically compare the use of IV versus oral acetaminophen in elderly patients undergoing TA-TAVR, the known inhibition of oral absorption and gastrointestinal motility associated with opioids suggests that IV administration of acetaminophen would be preferable to oral administration as a component of an MMA regimen in this vulnerable population.

## Limitations

This study has several limitations that should be considered when evaluating the results. Although the population studied seemed homogenous, with baseline characteristics of the IVA and non-IVA groups being similar, treatment assignment was not randomized. The duration of IVA administration was not standardized and was at the discretion of the heart team. Toward the end of the study period, there were significant cost-related pressures from the pharmacy to reduce the number of IVA doses to 4. In addition, this study did not assess rates of opioid-related ADEs and did not directly assess differences in overall cost of care between those who received and did not receive IVA for postoperative pain management. Finally, because this was a linear study evaluating outcomes before and after making a change in patient care, observed differences in LOS between groups may have been confounded by differences in patient selection, procedural refinement, or other unmeasured factors.

## CONCLUSIONS

Multimodal pain management incorporating IVA in patients undergoing TA-TAVR was associated with reduced narcotic use on the day of surgery and a shorter overall hospital LOS. Randomized trials are needed to directly assess the impact of IVA on opioid use and opioid-related complications in cardiac surgical patients.

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## CLINICAL PERSPECTIVE

This retrospective case series of 43 patients undergoing transapical transcatheter aortic valve replacement examined the feasibility of using intravenous acetaminophen for standard postoperative pain management, as compared with intravenous narcotics and oral narcotics/acetaminophen. They examined 20 patients who received intravenous acetaminophen and 23 patients who did not receive this medication. The patients who received intravenous acetaminophen used significantly fewer morphine equivalents on postoperative day 0 and had a shorter median hospital length of stay. They concluded that the use of intravenous acetaminophen may be beneficial in decreasing opioid use and length of stay in selected patients.

This is an interesting preliminary report, and similar to others, has suggested that intravenous acetaminophen may have benefits in shortening postoperative length of stay and narcotic use. However, this is an expensive drug and this was a very small retrospective case series that provided a relatively low level of evidence in support of usage of this drug. A larger, randomized trial would be of benefit.

 