

## Efficacy of Intravenous Acetaminophen as Adjunct Post-Operative Analgesic in Cardiac Surgery: A Retrospective Study

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### ABSTRACT

**Introduction.** The dose-dependent adverse events associated with post-operative opioid use may be reduced when opioids are used in conjunction with intravenous acetaminophen. The purpose of this study was to compare outcomes in median sternotomy patients receiving intravenous acetaminophen in addition to intravenous opioids versus intravenous opioids only.

**Methods.** A retrospective study was conducted on 122 adult patients undergoing median sternotomy at a regional tertiary-referral center. Data collected included patient demographics, length of stay, opioid and intravenous acetaminophen use, adverse effects, and transition time to oral pain medication.

**Results.** There was no difference between groups in demographics, preoperative risk scores, operative procedures, intravenous opioid consumption, transition time to oral pain medications, or length of stay. Acetaminophen use was associated with lower rates of atrial fibrillation (7.0% vs. 24.6%,  $p = 0.009$ ) and nausea/vomiting (8.9% vs. 32.3%,  $p = 0.002$ ), but higher rates of urinary retention (15.8% vs. 3.1%,  $p = 0.014$ ), constipation (50.0% vs. 20.0%,  $p = 0.001$ ) and respiratory depression (7.1% vs. 0.0%,  $p = 0.043$ ).

**Conclusion.** Intravenous acetaminophen was not associated with a reduction in length of stay or opioid consumption, but was associated with lower rates of atrial fibrillation, nausea, and vomiting. Additional studies are needed to determine if intravenous acetaminophen administration reduces atrial fibrillation in this population.

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### INTRODUCTION

The treatment of post-operative pain from median sternotomy in cardiac surgery patients has consisted primarily of opioid administration. Although effective, opioids are associated with dose-dependent adverse effects and negative outcomes possibly increasing length of hospital stay and subsequent healthcare costs.<sup>1</sup> Some of the common adverse effects associated with opioid use include respiratory depression, ileus, nausea, urinary retention, constipation, sedation, and addiction.<sup>1,2</sup> Multimodal analgesia approaches to post-operative pain management can minimize the undesirable adverse effects associated with the sole use of opioids.<sup>3,4</sup>

Intravenous acetaminophen (IA) received U.S. Food and Drug Administration approval in November 2010. It is a centrally acting analgesic and antipyretic. Intravenous acetaminophen has a very favorable side-effect profile and does not alter platelet aggregation factors or impose significant drug-drug interaction. Some of its common adverse effects include nausea, vomiting, headaches, and insomnia.<sup>5</sup> A vial of IA costs approximately \$45.00 per dose, whereas intravenous (IV) and oral narcotics cost approximately \$0.25 per dose at our facility. Although expensive, the use of IA could offset its associated cost-increase by reducing undesirable adverse effects, thereby shorten the length of hospital stays.<sup>5</sup>

Since its approval for use, studies in the gynecology and colorectal literature have shown reduced post-operative nausea and vomiting (PONV) and decreased hospital length of stay with the use of IA and adjunctive opioid analgesics in post-operative patients.<sup>6,7</sup> To our knowledge, only one study has been performed in post-operative cardiac patients in the United States to assess the efficacy of IA as an adjunct analgesic to opioids, but this study did not demonstrate a decrease in length of hospital stay as seen in other studies.<sup>8</sup>

The purpose of this study was to compare the length of hospitalization between median sternotomy patients who received IA in conjunction with oral and IV narcotics vs. IV and oral narcotics alone in the peri-operative period. Secondary data gathered in the study were used to compare IV opiate consumption, IA consumption, adverse effects, and time to transition from IV to oral pain medication.

### METHODS

We conducted a case-controlled, retrospective chart review of adult patients who presented to one midwestern tertiary-care hospital for non-emergency open cardiac surgery via median sternotomy from June 2014 to December 2015. In-hospital pharmacy records were searched to generate a list of all patients who underwent non-emergency open cardiac surgery via median sternotomy and received IA on the cardiothoracic intensive care unit (ICU) or floor during the study time period. The resultant patients were matched with case-control patients who underwent non-emergency open cardiac surgery via median sternotomy and did not receive IA in the post-operative period. Cases and controls were matched based on age, sex, race, and body mass index. Patient charts were reviewed to collect additional data for analysis.

Data collected included patient's age, race/ethnicity, gender, body mass index, pertinent medical history, preoperative risk score, IV and oral opiate consumption, IA consumption, adverse effects, time to transition from IV to oral pain medication, and hospital outcomes (ICU days, ventilator days, and hospital length of stay). Patient medical histories were reviewed to exclude patients who were on scheduled narcotics or had a history of narcotic dependence prior to surgery. Patients with severe hepatic impairment also were excluded. Severe hepatic impairment was defined as a Child class B or C.

All doses of opioids administered during the hospitalization were tallied and converted to milligrams of morphine based on opioid equivalence per day. Intravenous acetaminophen was measured in milligram per day and was administered post-operatively every

six hours for 24–48 hours. For the purposes of this study, only medications (opioids and IA) administered in the peri-operative time period were quantified until each patient was discharged from the hospital.

**Statistical Analysis.** Comparisons of qualitative and quantitative data between subgroups were compared using chi-square analysis and analysis of variance. Non-parametric comparisons were used when assumptions for data distributions could not be met. All statistical tests were two-sided and considered statistically significant when  $p \leq 0.05$ . All analyses were conducted using SPSS release 19.0 (IBM Corp., Armonk, New York).

This study was approved for implementation by the Institutional Review Board of Via Christi Hospitals Wichita Inc.

## RESULTS

A total of 146 patient charts were reviewed for study inclusion ( $n = 73$  for each group). Of those, eight patients were excluded from the opioids only group; one with a history of severe hepatic impairment and seven for narcotic dependence. Seventeen patients were excluded from the opioids + IA group for a history of narcotic dependence. One patient underwent two surgeries in which opioid and IA were used in the post-operative period, so their second surgery was considered a separate case for analysis. The total number of patients included in analysis after exclusions was 122, with 65 patients (53.3%) in the opioid only group, and 57 patients (46.7%) in the opioids + IA group.

Demographics, pertinent past medical history, and preoperative risk scores were not significantly different between groups, though there was a trend for higher risk patients to have received IA (Table 1). Intravenous opioids administered and time to transition to oral pain regimen were not different between study groups (Table 2). Patients who received IA had higher rates of respiratory depression (7.1% vs. 0.0%,  $p = 0.043$ ), urinary retention (15.8% vs. 3.1%,  $p = 0.014$ ), and constipation (50.0% vs. 20.0%,  $p = 0.001$ ). However, there was a significant reduction in the incidence of PONV with the use of IA (8.9% vs. 32.3%,  $p = 0.002$ ). Additionally, there was a significant decrease in the incidence of atrial fibrillation in patients that received IA in conjunction with opioids (7.0% vs. 26.2%,  $p = 0.005$ ) as shown in Table 2. When looking only at patients that had undergone a coronary artery bypass graft (CABG) procedure, the decreased incidence of atrial fibrillation in patients that received IA in conjunction with opioids remained significant (7.3% vs. 29.3%,  $p = 0.010$ ). Other less common adverse events associated with each group are shown in Table 3. A breakdown of procedures performed in patients in the opioid only group and the IA group are shown in Table 4.

The primary study outcome was length of hospital stay. Our data did not demonstrate a clinically significant reduction in median length of hospital stay with use of adjunct IA compared with opioid use alone (6 vs. 6 days respectively,  $p = 0.059$ ; Table 5). Intensive care unit days, and ventilator days were also similar between the two groups.

**Table 1. Demographics and pertinent medical history of individuals who received opioid only or opioid with intravenous acetaminophen following median sternotomy.\***

Parameter	Opioid only group	Opioid + IA group	p-Value
Number of observations	65 (53.3%)	57 (46.7%)	---
Age (years)	67.3 ± 11.1	68.5 ± 9.7	0.544
Body mass index	29.6 ± 5.2	29.5 ± 6.6	0.954
Male sex	50 (76.9%)	36 (63.2%)	0.096
Race†			0.465
White	58 (92.1%)	49 (89.1%)	
Black	2 (3.2%)	1 (1.8%)	
Asian	3 (4.8%)	3 (5.5%)	
Hispanic	0 (0.0%)	2 (3.6%)	
History of hepatic impairment	1 (1.5%)	1 (1.8%)	> 0.999
Preoperative Risk Score‡	0.013 (0.007,0.020)	0.017 (0.010,0.030)	0.083

\*Data are presented as N (%), mean ± standard deviation, or median (25th, 75th percentiles).

†Two patients from each group chose not to disclose race.

‡Risk score values based on 48 individuals in the opioid only group and 46 individuals in the opioid and IA group.

**Table 2. Pain management and adverse effects for individuals who received opioid only or opioid with intravenous acetaminophen following median sternotomy.\***

Parameter	Opioid only group	Opioid + IA group	p-Value
Number of observations	65 (53.3%)	57 (46.7%)	---
IV opioid consumption (mg in morphine equivalents)	14 (4,27)	14 (8,24)	0.470
IA consumption (g)	n/a	6.1 ± 2.1	n/a
Time to transition to oral pain medications (hr)	31 (10,51.5)	38 (16.5,65)	0.399
Post-operative nausea/vomiting	21 (32.3%)	5 (8.9%)	0.002
Atrial fibrillation	17 (26.2%)	4 (7.0%)	0.005
Constipation	13 (20.0%)	28 (50.0%)	0.001
Urinary retention	2 (3.1%)	9 (15.8%)	0.014
Respiratory depression	0 (0.0%)	4 (7.1%)	0.043
Ileus	0 (0.0%)	0 (0.0%)	n/a
Other adverse effects	7 (10.8%)	6 (10.5%)	0.965

\*Data are presented as N (%), mean ± standard deviation, or median (25th, 75th percentiles).

†Fisher's exact test used due to expected cell counts <5.

**Table 3. A list of “other adverse effects” for individuals who received opioid only or opioid with intravenous acetaminophen following median sternotomy.**

Study group	Other adverse effects
Opioid only group (n=7)	Confusion (4) Lightheadedness (2) Ventricular tachycardia (1)
Opioid + IA group (n=6)	Dizziness (1) Headache (1) Bronchitis (1)* Acute kidney injury (1)* Clostridium difficile (1) Death (2)

\*Bronchitis and acute kidney injury were experienced by the same patient.

**Table 4. Operative procedures for individuals who received opioid only and opioid with intravenous acetaminophen following median sternotomy.**

Procedure(s)	Opioid only Group N (%)	Opioid + IA group N (%)
Number of observations	65 (53.3%)	57 (46.7%)
CABG	41 (63.1%)	41 (71.9%)
AVR	7 (10.8%)	7 (12.3%)
MVR	0 (0.0%)	2 (3.5%)
CABG + AVR	6 (9.2%)	1 (1.8%)
CABG + MVR	0 (0.0%)	1 (1.8%)
CABG + valve +RFA/LAA	3 (4.6%)	2 (3.5%)
CABG+ RFA/LAA	4 (6.2%)	0 (0.0%)
CABG + MVR +AVR	0 (0.0%)	2 (3.%)
MVR + AVR	1 (1.5%)	0 (0.0%)
MV + RFA/LAA	1 (1.5%)	0 (0.0%)
Other	2 (3.1%)	1 (1.8%)

CABG = coronary artery bypass graft; AVR = aortic valve replacement; MVR = mitral valve replacement; RFA = radio frequency ablation; LAA = left atrial appendage; MV = mitral valve.

**Table 5. A comparison of length of stay outcomes for individuals who received opioid only or opioid with intravenous acetaminophen following median sternotomy.\***

Parameter	Opioid only group	Opioid + IA group	p-Value
Number of observations	65 (53.3%)	57 (46.7%)	---
Intensive care unit days	3 (2,4)	2 (2,4)	0.286
Ventilator days†	1 (1,4)	1 (1,2.5)	0.758
Hospital length of stay	6 (5,7)	6 (5,8)	0.059‡

\*Data are presented as N (%), or median (25th, 75th percentiles).

†Only individuals with non-zero values used for analysis.

‡Test of medians with Yates correction for continuity.

## DISCUSSION

**Analgesic and Opiate Consumption Effects.** Studies on the efficacy of IA have demonstrated conflicting results. For example, Cattabriga et al.<sup>9</sup> demonstrated a significant improvement in analgesic effect with IA within the first 24 hours and a 49% reduction in cumulative morphine consumption within the first three days in post median sternotomy patients. Other studies also have found a significant reduction in mean opioid consumption in otorhinolaryngology and gynecology patients who received IA.<sup>6,10</sup> Those studies were inconsistent with our results, as we found no change in the cumulative opioid consumption with adjunctive IA use. Similar to our study, others have demonstrated no reduction in the mean opioid consumption with addition of IA.<sup>7,11</sup> This discrepancy in results could be explained by the lack of standardization of IA administration. In our study, the total duration of the IA administration varied between patients, ranging anywhere between 24-48 hours (4-8g of IA), partly due to the financial implications associated with the IV formulation. According to Remy et al.,<sup>12</sup> the typical administration of 1 g of IA every six hours, as described in many of the studies reviewed, has less than 10 mg sparing effect on IV opioid consumption over a 24-hour period. A study by Juhl and colleagues supported this theory by demonstrating that 2 g IA every six hours (total daily dose maximum of 8 g) was superior to 1 g of IA every six hours in terms of efficacy and analgesia.<sup>13</sup> This is important, as it may explain why opioid consumption was not found to decrease given the lower dose of analgesia achieved by 1 g of IA in our study. Hence, a stronger dose of IA every six hours may be needed to reach an effective therapeutic dose as suggested by Remy et al.<sup>2</sup>

**Hospital Length of Stay Effects.** Two non-cardiac surgery studies demonstrated a significantly shorter hospital length of stay of one to two days with the use of IA compared to placebo.<sup>6,14</sup> The only U.S. cardiac study by Mamoun et al.<sup>7</sup> revealed no effect on hospital length of stay in addition to ventilation days, ICU, or opioid consumption with adjunct use of IA, which is similar to our results. The discrepancy of the length of hospital stay likely is due to the different patient populations; inherently cardiac surgery patients have higher peri-operative risk scores and worse co-morbidities that are less likely to be affected by the addition of IA or reduction of opioid consumption.

**Post-operative Nausea and Vomiting Effects.** We demonstrated a significant reduction in PONV with the use of IA consistent with the meta-analysis performed by Apfel and colleagues.<sup>15</sup> However, the amount of opioids administered did not differ between the two groups. This contradicted the study performed by Lahtinen and colleagues<sup>16</sup>, who demonstrated decreased opiate consumption in the first 24 hours, but no difference in PONV, with the administration of Propacetamol, a prodrug of acetaminophen. Although our study did not measure pain scores, the combination of IA and opioids possibly provided more effective analgesia, which is believed to decrease the incidence of PONV indirectly. In addition, according to Apfel et al.<sup>15</sup>, IA given prophylactically in a scheduled manner has been shown to be effective in reducing PONV. They further suggested that IA has a direct antiemetic effect on the brain leading to less PONV.

**Other Adverse Effects.** Urinary retention, constipation, and respiratory depression were significantly higher in the IA group, which has not been demonstrated in other studies. Adverse effects of IA less than 1%, according to its manufacturer's label, included respiratory atelectasis, pulmonary edema, and constipation. Although those are very low percentages, the use of opioids in conjunction with IA may have synergistic effects that could potentiate those adverse effects.

**Atrial Fibrillation Reduction.** Incidentally, we observed a lower occurrence of atrial fibrillation in the group receiving IA, an effect that has not been reported in other studies with IA. Both groups had similar indications and preoperative risk factors, which in theory should minimize confounding factors. Interestingly, according to animal studies, acetaminophen has been found to have cardioprotective and antiarrhythmic effects by attenuating release of free radicals due to oxidative injuries.<sup>17,18</sup> According to Chang et al.,<sup>19</sup> the addition of IA may inhibit nitric oxide release, which would enhance diastolic tension thereby resulting in improved inotropic effect and improved electromechanical cardiac activity leading to less cardiac arrhythmias. Whether IA plays a definite role in the prevention of atrial fibrillation in post cardiac surgery patients remains to be evaluated in a prospective study.

**Limitations.** Being a retrospective study, we were limited to the data available to us at this institution and some data points were missing in a few patients such as preoperative risk factors. Furthermore, there was a concern for selection bias by the surgeons, as we noted earlier a trend for higher risk patients to receive IA. In addition, although we excluded patients with history of narcotic use, the accuracy of medical records or reliability of individuals could be questioned as well. Moreover, the administration of IA was not standardized. Hence, a larger prospective study that compares several administration protocols is necessary to establish a safe effective therapeutic dose. Lastly, our observation of decreased rates of atrial fibrillation was incidental and should be further studied in humans to confirm such findings. Although it may prove initially to be costly, the use of prophylactic IA to prevent atrial fibrillation may offset its associated cost-increase in the long run. A prospective randomized controlled trial is needed to validate this hypothesis.

## CONCLUSIONS

Intravenous acetaminophen was not associated with a reduction in the length of hospital stay or intravenous opioid consumption in post-median sternotomy patients at this community-based, tertiary-care facility. However, IA was associated with a reduction in other adverse side effects such as atrial fibrillation and PONV. The use of IA may play a role in atrial fibrillation prevention; however, additional studies are needed to support this conclusion.

## REFERENCES

- Oderda GM, Evans RS, Lloyd J, et al. Cost of opioid-related adverse drug events in surgical patients. *J Pain Symptom Manage* 2003; 25(3):276-283. PMID: 12614962.
- Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: Meta-analysis of randomized controlled trials. *Br J Anaesth* 2005; 94(4):505-513. PMID: 15681586.
- Memis D, Inal MT, Kavalci G, Sezer A, Sut N. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in intensive care unit. *J Crit Care* 2010; 25(3):458-462. PMID: 20189753.
- Smith HS. Perioperative intravenous acetaminophen and NSAIDs. *Pain Med* 2011; 12(6):961-981. PMID: 21627768.
- Yeh YC, Reddy P. Clinical and economic evidence for intravenous acetaminophen. *Pharmacotherapy* 2012; 32(6):559-579. PMID: 22570116.
- Arici S, Gurbet A, Türker G, Yavaşcaoglu B, Sahin S. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. *Agri* 2009; 21(2):54-61. PMID: 19562533.
- Mamoun NF, Lin P, Zimmerman NM, et al. Intravenous acetaminophen analgesia after cardiac surgery: A randomized, blinded, controlled superiority trial. *J Thorac Cardiovasc Surg* 2016; 152(3):881-889. PMID: 27236864.
- Turan A, Karimi N, Zimmerman NM, et al. Intravenous acetaminophen does not decrease persistent surgical pain after cardiac surgery. *J Cardiothorac Vasc Anesth* 2017; 31(6):2058-2064. PMID: 29066145.
- Cattabriga I, Pacini D, Lamazza G, et al. Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: A double blind randomized controlled trial. *Eur J Cardiothorac Surg* 2007; 32(3):527-531. PMID: 17643995.
- Atef A, Fawaz AA. Intravenous paracetamol is highly effective in pain treatment after tonsillectomy in adults. *Eur Arch Otorhinolaryngol* 2008; 265(3):351-355. PMID: 17891409.
- Cakan T, Inan N, Culhaoglu S, Bakkal K, Başar H. Intravenous paracetamol improves the quality of postoperative analgesia but does not decrease narcotic requirements. *J Neurosurg Anesthesiol* 2008; 20(3):169-173. PMID: 18580346.
- Remy C, Marret E, Bonnet F. State of art of paracetamol in acute pain therapy. *Curr Opin Anaesthesiol* 2006; 19(5):562-565. PMID: 16960492.
- Juhl GI, Norholt SE, Tonnesen E, Hiesse-Provost O, Jensen TS. Analgesic efficacy and safety of intravenous paracetamol (acetaminophen) administered as a 2 g starting dose following third molar surgery. *Eur J Pain* 2006; 10(4):371-377. PMID: 16085437.
- Zafar N, Davies R, Greenslade GL, Dixon AR. The evolution of analgesia in an 'accelerated' recovery programme for resectional laparoscopic colorectal surgery with anastomosis. *Colorectal Dis* 2010; 12(2):119-124. PMID: 19207712.
- Apfel CC, Turan A, Souza K, Pergolizzi J, Hornuss C. Intravenous acetaminophen reduces postoperative nausea and vomiting: A systematic review and meta-analysis. *Pain* 2013; 154(5):677-689. PMID: 23433945.
- Lahtinen P, Kokki H, Hendolin H, Hakala T, Hynynen M. Propacetamol as adjunctive treatment for postoperative pain after cardiac surgery. *Anesth Analg* 2002; 95(2):813-819. PMID: 12351250.
- Merrill GF, Merrill JH, Golfetti R, et al. Antiarrhythmic properties of acetaminophen in the dog. *Exp Biol Med (Maywood)* 2007; 232(9):1245-1252. PMID: 17895533.
- Jaques-Robinson KM, Golfetti R, Baliga SS, Hadzimichalis NM, Merrill GF. Acetaminophen is cardioprotective against H2O2-induced injury in vivo. *Exp Biol Med (Maywood)* 2008; 233(10):1315-1322. PMID: 18703752.
- Chang JH, Cheng PY, Hsu CH, Chen YC, Hong PD. Effects of acetaminophen on left atrial contractility. *Acta Cardiol Sin* 2016; 32(4):485-490. PMID: 2747136.

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