Intravenous Acetaminophen Does Not Decrease Persistent Surgical Pain After Cardiac Surgery

Alparslan Turan, MD*, 1, Nika Karimi, MD*, Nicole M. Zimmerman, MS*, †, Stephanie L. Mick, MD‡, Daniel I. Sessler, MD*, Negmeldeen Mamoun, MD§

*Department of Outcomes Research, Anaesthesiology Institute, Cleveland Clinic, Cleveland, OH
†Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH
‡Department of Cardiothoracic Surgery, Cleveland Clinic, Cleveland, OH
§Departments of Cardiothoracic Anaesthesiology and Outcomes Research, Anaesthesiology Institute, Cleveland Clinic, Cleveland, OH

Objective: The authors investigated the hypothesis that perioperative acetaminophen reduces incisional pain at 30 and 90 days.

Design: This was a prospective, randomized, double-blind trial.

Setting: Tertiary-care hospital (single center) cardiac surgery unit.

Participants: Patients undergoing cardiac surgery via median sternotomy.

Interventions: Patients were assigned randomly to intravenous (IV) acetaminophen or IV placebo. Patients were given 4 doses of 1 g of IV acetaminophen or an equal volume of saline placebo over 15 minutes every 6 hours for 24 hours starting in the operating room after sternal closure.

Measurements and Main Results: Study participants were assessed by phone for incisional pain severity 30 and 90 days after surgery. Those reporting any incisional pain were asked to complete the Neuropathic Pain Questionnaire—Short Form and the modified Brief Pain Inventory.

Patients were compared on 30- and 90-day incisional pain severity using separate multivariable linear regression models. IV acetaminophen had no effect on 30- and 90-day incisional pain, with an estimated difference in means (confidence interval) of 0.06 (–0.87 to 0.99) at 30 days (p = 0.88) and 0.07 (–0.71 to 0.86) at 90 days (p = 0.83). Low pain severity, neuropathic pain, and interference at both 30 and 90 days after surgery, regardless of treatment group, were observed.

Conclusions: IV acetaminophen did not reduce the incidence or intensity of incisional pain at 30 days and 90 days after surgery.

© 2017 Elsevier Inc. All rights reserved.

Key Words: acetaminophen; pain; postoperative; thoracic surgery

CARDIAC SURGICAL PROCEDURES are among the common surgeries performed worldwide. About 10% to 50% of patients report persistent incisional pain after cardiac surgery, with at least one-third of the persistent pain being moderate-to-severe in intensity, which substantially reduces quality of life. Persistent incisional pain results from nerve injury concomitant with tissue injury secondary to surgical dissection and deleterious factors relating to the healing process. The consequent pain signals activate nociceptive pathways in the central nervous system, which provoke restructuring and central sensitization, a process that is maintained by peripheral input. Consistent with this mechanism, there is a strong association between the intensity of acute postoperative pain and the risk of developing persistent incisional pain.

Acetaminophen is a justifiably popular nonopioid analgesic. The Food and Drug Administration approval of an intravenous (IV) formulation has increased use of the drug as a component of...
perioperative multimodal analgesia. In a recent study, IV acetaminophen was evaluated in a pooled analysis of randomized controlled trials. Patients given acetaminophen had better acute postoperative pain control which, in turn, was the strongest predictor for improved patient satisfaction. The few published studies that used acetaminophen after cardiac surgery have reported reductions in acute postoperative pain scores (25%-35%) and opioid consumption (40%-50%).

However, there are additional mechanisms by which the drug may reduce development of persistent incisional pain. The mechanisms by which acetaminophen decreases pain are complex, and multiple central paths appear to contribute. Acetaminophen inhibits prostaglandins via the cyclooxygenase pathway, activates cannabinoid CB1 receptors, and inhibits nitric oxide pathways. Acetaminophen also has peripheral action, whereby it can reduce prostaglandin E2 release from the surgical site. Acetaminophen reduces acute postoperative pain and possibly blunts various pathways that contribute to acute pain becoming chronic. Thus, there are compelling reasons to believe that perioperative acetaminophen administration may decrease persistent incisional pain after cardiac surgery. The authors, therefore, tested the hypothesis that perioperative IV acetaminophen is associated with incisional pain at 30 and 90 days.

Methods

This was a preplanned substudy of the authors’ prospective, single-center, randomized, parallel-group, and double-blind trial examining the effect of IV acetaminophen on postoperative pain scores and opioid consumption within 24 hours after surgery. In that study, acetaminophen was superior to placebo on mean pain intensity scores and noninferior to opioid consumption, with estimated difference in mean pain (95% confidence interval [CI]) of −0.90 (−1.39 to −0.42; \( p < 0.001 \) [superior]) and an estimated ratio of means in opioid consumption (90% CI) of 0.89 (0.73–1.10; \( p = 0.28 \) [noninferior; not superior]). The trial was approved by the Cleveland Clinic Institutional Review Board and registered on ClinicalTrials.gov on March 28, 2013 (NCT01822821). All patients signed informed consent.

The protocol is detailed in the companion report. Briefly, patients scheduled for primary coronary artery bypass grafting or isolated valve replacement via a median sternotomy were included. Patients were excluded for previous cardiac surgery; complex cardiac surgery, including coronary artery bypass grafting combined with valve replacement; multiple valve replacements; and aortic arch surgery. Other exclusion criteria included weight <50 kg, preoperative renal insufficiency or patients requiring hemodialysis, history of liver cirrhosis or active liver disease, chronic pain conditions requiring daily preoperative opioid administration, pregnancy, or allergy to acetaminophen or fentanyl.

Standard anesthesia care included routine American Society of Anesthesiologists-recommended monitors, invasive arterial pressure, central venous pressure, transesophageal echocardiography, and bladder temperature monitoring. Patients were randomized (1:1) without stratification to IV acetaminophen or placebo. Allocations were concealed by a password-protected website. Randomization codes were computer generated using the PLAN procedure in SAS statistical software (SAS Institute, Cary, NC). The randomization was accessed shortly before induction of anesthesia to conceal allocation as long as practical. Patients were given 4 doses of 1 g of IV acetaminophen or an equal volume of saline placebo over 15 minutes every 6 hours for 24 hours. The initial dose was given in the operating room after sternal closure. All the drugs were prepared by pharmacy staff, and investigators blinded to drug allocation performed the evaluations.

All patients were offered patient-controlled analgesia (PCA) postoperatively. Fentanyl was the default drug (PCA settings: no basal rate, demand bolus dose of 20 \( \mu \)g, bolus interval every 6 min). However, hydromorphone was used (PCA settings: no basal rate, demand bolus dose of 0.2 mg, bolus interval every 6 min) if the patient had an allergy to fentanyl or if clinically indicated. Rescue analgesia included IV fentanyl or hydromorphone boluses or oral oxycodone if inadequately controlled with PCA. IV meperidine was given as needed for shivering. Wounds were not infiltrated with local anesthetics. Other analgesics were not permitted, such as topical lidocaine patches and nonsteroidal anti-inflammatory drugs, and neither were drugs containing acetaminophen such as Percocet (acetaminophen and oxycodone) and Vicodin (acetaminophen and hydrocodone) to avoid exceeding the maximum allowable dose of acetaminophen.

Study participants were assessed by phone for incisional pain 30 and 90 days after surgery. Those reporting any incisional pain were asked to complete the Neuropathic Pain Questionnaire—Short Form and the modified Brief Pain Inventory.

Primary Analyses

The balance of randomized groups was assessed for potentially confounding baseline variables using absolute standardized difference, defined as the absolute difference in means or proportions divided by the pooled standard deviation. Balance refers to how similar the IV acetaminophen and placebo groups were on patient characteristics. A priori, variables with absolute standardized difference >0.2 were defined as imbalanced between groups and adjusted for in the following analyses. All substudy analyses were per protocol, only including patients who completed 30- or 90-day follow-ups. Missing follow-ups were assumed to be missing at random and occurred independently of treatment assignment.

Incisional pain was assessed at 30 and 90 days after surgery using a numeric rating scale (NRS), for which 0 is no pain and 10 is the worst possible pain. Pain scores were assumed to be normally distributed. Thus, the effect of IV acetaminophen on...
considered to be imbalanced and adjusted for in all analyses.

and diabetes.

pacemaker wire removal, and coronary atrial or tricuspid valve mass excision, aortic root repair or aortoplasty, left atrial appendage ligation, Maze surgery, pulmonary vein isolation, right

4

assigned randomly to receive placebo, fewer patients completed the 30- and 90-day follow-ups.

NOTE. Summary statistics are reported as mean ± standard deviation and median [Q1-Q3], as appropriate.

Table 1 Baseline and Demographic Characteristics of Complete Study Population

<table>
<thead>
<tr>
<th>Factor</th>
<th>Acetaminophen (n = 73)</th>
<th>Placebo (n = 74)</th>
<th>ASD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62 ± 14</td>
<td>59 ± 14</td>
<td>0.22</td>
</tr>
<tr>
<td>Female (%)</td>
<td>24 (33)</td>
<td>24 (32)</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30 ± 6</td>
<td>30 ± 6</td>
<td>0.08</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>47 (64)</td>
<td>47 (64)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>14 (19)</td>
<td>5 (7)</td>
<td>0.38</td>
</tr>
<tr>
<td>Procedure information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve surgery (%)</td>
<td>36 (49)</td>
<td>37 (50)</td>
<td>0.01</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>21 (29)</td>
<td>17 (23)</td>
<td>0.13</td>
</tr>
<tr>
<td>Myectomy (%)</td>
<td>24 (33)</td>
<td>18 (24)</td>
<td>0.19</td>
</tr>
<tr>
<td>Ascending aortic replacement (%)</td>
<td>15 (21)</td>
<td>17 (23)</td>
<td>0.06</td>
</tr>
<tr>
<td>Other surgery (%)†</td>
<td>23 (32)</td>
<td>17 (23)</td>
<td>0.19</td>
</tr>
<tr>
<td>Cardiopulmonary bypass (%)</td>
<td>73 (100)</td>
<td>74 (100)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intraoperative fentanyl dose (µg)</td>
<td>1.021 ± 230</td>
<td>1.018 ± 352</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviations: ASD, absolute standardized difference; BMI, body mass index; CABG, coronary artery bypass graft surgery.

*ASD is defined as the absolute difference in means or proportions divided by the pooled standard deviation. Any variables with ASD > 0.20 were considered to be imbalanced and adjusted for in all analyses.

†Other surgeries include atrial septal defect or patent foramen ovale closure, left atrial appendage ligation, Maze surgery, pulmonary vein isolation, right atrial or tricuspid valve mass excision, aortic root repair or aortoplasty, pacemaker wire removal, and coronary fistula repair.

30- and 90-day incisional pain scores was assessed using separate multivariable linear models.

Because observed pain scores appeared skewed (ie, few patients had very high pain scores and the majority had low or no postoperative pain), a sensitivity analysis using nonparametric techniques was performed. The effect of IV acetaminophen on 30- and 90-day incisional pain scores with separate 2-sample Wilcoxon rank sum tests was assessed, using the

Hodges-Lehmann test to estimate the location shift between randomized groups.

Descriptive Analyses

The incidence of any incisional pain at 30 and 90 days after surgery (ie, pain score > 0) is reported. In addition, neuropathic pain, median [Q1-Q3] pain severity, and median [Q1-Q3] pain interference for patients who reported incisional pain during a follow-up also are described.

An alpha of 0.05 was used for the primary and sensitivity analyses, with a significance criterion of 0.025 for each primary and sensitivity analysis to control for multiple comparisons (ie, Bonferroni correction [0.05/2]).

Sample Size and Power

Even though this subanalysis was planned a priori, the trial was not powered for this subanalysis. This was a post-hoc empirical power analysis based on the number of patients who completed follow-ups. With 52 patients in the IV acetaminophen group and 60 control patients completing the 30-day follow-up and an observed mean ± standard deviation (SD) control group 30-day incision pain score of 2.7 ± 2.0, there was 74% empirical power to detect a 1-point decrease in 30-day incisional pain and 26% empirical power to detect a 0.5-point decrease in 30-day pain. Similarly, with 50 patients in the IV acetaminophen group and 55 control patients completing 90-day follow-up and an observed mean ± SD control group 90-day incisional pain score of 1.0 ± 1.8, there was 70% empirical power to detect at least a 1-point decrease in 90-day pain and 25% power to detect a 0.5-point decrease in pain.

Results

A total of 1,845 patients were screened between May 2013 and December 2014, of whom 155 consented to participate. Five of the consenting patients were excluded from the study before randomization because surgery was cancelled or the

Table 2 Effect of IV Acetaminophen (Versus Control) on Chronic Incisional Pain

<table>
<thead>
<tr>
<th>Primary Analyses</th>
<th>n*</th>
<th>IVA (n = 73)</th>
<th>Placebo (n = 74)</th>
<th>Difference in Means† (CI)‡ IVA–Placebo</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-d incisional pain</td>
<td>52</td>
<td>2.8 ± 2.1</td>
<td>2.7 ± 2.0</td>
<td>0.06 [0.07 to 0.99]</td>
<td>0.88</td>
</tr>
<tr>
<td>90-d incisional pain</td>
<td>50</td>
<td>1.1 ± 1.6</td>
<td>1.0 ± 1.8</td>
<td>0.07 [0.07 to 0.86]</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Nonparametric Sensitivity Analyses

| 30-d incisional pain | 52 | 3.0 [1.0 to 4.0] | 2.0 [1.5 to 4.0] | 0.0 [–1.0 to 1.0] | 0.67     |
| 90-d incisional pain | 50 | 0.0 [0.0 to 2.0] | 0.0 [0.0 to 1.0] | 0.0 [0.0 to 0.0] | 0.82     |

NOTE. Summary statistics are reported as mean ± standard deviation and median [Q1-Q3], as appropriate.

*Number of patients included in the analysis for each group. Although 73 patients were assigned randomly to receive IV acetaminophen and 74 patients were assigned randomly to receive placebo, fewer patients completed the 30- and 90-day follow-ups.

†Difference in mean incisional pain among IV acetaminophen versus placebo patients estimated from a multivariable linear regression model adjusting for age and diabetes.

‡Significance criterion of 0.025 used for each outcome to adjust for multiple comparisons (ie, Bonferroni correction [0.05/2]).

§A nonparametric sensitivity analysis was performed because observed pain scores appeared skewed. Difference in medians of IV acetaminophen versus placebo patients estimated using the Wilcoxon rank sum test and the Hodges-Lehmann estimator of location shift between groups.
surgical plan was changed; 150 patients thus completed enrollment. Among the 150 patients enrolled in the trial (75 patients per group), 2 patients in the acetaminophen group and 1 patient in the placebo group were excluded from analyses because they withdrew from the trial before receiving the study intervention.

Baseline and demographic characteristics were similar (Table 1). However, patients in the IV acetaminophen group had more diabetes mellitus and were older based on the a priori definition of imbalance (ie, absolute standardized difference exceeding 0.2), so the authors adjusted for diabetes status and age in the following analyses.

Pain assessments at 30 days were completed by 52 of 73 IV acetaminophen (71%) and 60 of 74 placebo (81%) patients. Thirty-day incisional pain was reported in 77% of IV acetaminophen and 78% of placebo patients completing follow-up. Thirty-day mean ± SD pain scores were 2.8 ± 2.1 for IV acetaminophen and 2.7 ± 2.0 for placebo patients. IV acetaminophen was not associated with 30-day incisional pain compared with placebo, with an estimated difference in means (CI) of 0.06 (–0.87 to 0.99; p = 0.88) (Table 2). Among those reporting pain, the mean intensity was 3.4 ± 1.7 for IV acetaminophen and 3.6 ± 1.7 for placebo patients. Thirty-day neuropathic incisional pain incidence was 8% among IV acetaminophen and 12% among placebo patients.

Fifty of 73 IV acetaminophen (68%) and 55 of 74 placebo patients (74%) completed 90-day follow-up, reporting mean ± SD pain scores of 1.1 ± 1.6 and 1.0 ± 1.8, respectively. Ninety-day incisional pain was reported among 40% of IV acetaminophen and 42% of placebo patients completing follow-up. Among those reporting pain, the mean intensity was 2.8 ± 1.3 for IV acetaminophen and 2.5 ± 2.1 for placebo patients. IV acetaminophen also was not associated with 90-day incisional pain compared with placebo, with an estimated difference in means (CI) of 0.07 (–0.71 to 0.86; p = 0.83). Neuropathic incisional pain was reported in 0% of IV acetaminophen and 2% of control patients 90 days after surgery.

The nonparametric sensitivity analyses also failed to find an association between IV acetaminophen and 30- and 90-day pain scores (see Table 2). Low pain severity and little interference in life at both 30 and 90 days after surgery were observed (Tables 3 and 4; Fig 1). No substantial differences in pain severity or interference were observed between treatment groups.

Discussion

Pain frequently was reported at 30 days (74%) and the intensity was mild-to-moderate, at about 3.5 on a 0-to-10-point NRS. The high prevalence of incisional pain at 30 days was perhaps unsurprising because this timeframe is well within the

<table>
<thead>
<tr>
<th>30-Day Assessment</th>
<th>IV Acetaminophen (n = 52)</th>
<th>Placebo (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients reporting any incisional pain, n (%)</td>
<td>40 (77)</td>
<td>47 (78)</td>
</tr>
<tr>
<td>Neuropathic incisional pain, n (%)</td>
<td>4 (8)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Overall incisional pain severity†‡</td>
<td>Mean ± SD 1.8 ± 1.5</td>
<td>1.6 ± 1.5</td>
</tr>
<tr>
<td>Median [Q1-Q3] 1.5 [0.8-2.6]</td>
<td>1.1 [0.5-2.5]</td>
<td></td>
</tr>
<tr>
<td>Worst pain in the past 24 h†</td>
<td>Mean ± SD 3.3 ± 2.2</td>
<td>3.1 ± 2.7</td>
</tr>
<tr>
<td>Median [Q1-Q3] 3.0 [2.0-4.0]</td>
<td>2.0 [1.0-5.0]</td>
<td></td>
</tr>
<tr>
<td>Least pain in the past 24 h‡</td>
<td>Mean ± SD 0.6 ± 1.0</td>
<td>0.7 ± 1.2</td>
</tr>
<tr>
<td>Median [Q1-Q3] 0.0 [0.0-1.0]</td>
<td>0.0 [0.0-1.0]</td>
<td></td>
</tr>
<tr>
<td>Average pain in the past 24 h†</td>
<td>Mean ± SD 2.0 ± 1.5</td>
<td>1.9 ± 1.8</td>
</tr>
<tr>
<td>Median [Q1-Q3] 2.0 [1.0-3.0]</td>
<td>2.0 [0.0-3.0]</td>
<td></td>
</tr>
<tr>
<td>Current pain†</td>
<td>Mean ± SD 1.3 ± 1.9</td>
<td>0.8 ± 1.5</td>
</tr>
<tr>
<td>Median [Q1-Q3] 0.0 [0.0-2.5]</td>
<td>0.0 [0.0-1.0]</td>
<td></td>
</tr>
<tr>
<td>Overall Incisional pain interference†‡</td>
<td>Mean ± SD 1.4 ± 1.2</td>
<td>1.3 ± 1.9</td>
</tr>
<tr>
<td>Median [Q1-Q3] 1.1 [0.4-1.9]</td>
<td>0.6 [0.0-2.0]</td>
<td></td>
</tr>
<tr>
<td>General activity interference†</td>
<td>Mean ± SD 1.8 ± 2.1</td>
<td>1.5 ± 2.5</td>
</tr>
<tr>
<td>Median [Q1-Q3] 1.0 [0.0-2.5]</td>
<td>0.0 [0.0-2.0]</td>
<td></td>
</tr>
<tr>
<td>Mood interference†</td>
<td>Mean ± SD 1.1 ± 1.6</td>
<td>1.1 ± 2.2</td>
</tr>
<tr>
<td>Median [Q1-Q3] 1.0 [0.0-1.0]</td>
<td>0.0 [0.0-1.0]</td>
<td></td>
</tr>
<tr>
<td>Walking ability interference†</td>
<td>Mean ± SD 0.8 ± 1.4</td>
<td>1.1 ± 2.2</td>
</tr>
<tr>
<td>Median [Q1-Q3] 0.0 [0.0-1.0]</td>
<td>0.0 [0.0-1.0]</td>
<td></td>
</tr>
<tr>
<td>Normal work interference‡</td>
<td>Mean ± SD 1.9 ± 2.0</td>
<td>2.3 ± 3.1</td>
</tr>
<tr>
<td>Median [Q1-Q3] 2.0 [0.0-3.0]</td>
<td>1.0 [0.0-4.0]</td>
<td></td>
</tr>
<tr>
<td>Interference of relations with other people†</td>
<td>Mean ± SD 0.7 ± 1.1</td>
<td>0.4 ± 1.1</td>
</tr>
<tr>
<td>Median [Q1-Q3] 0.0 [0.0-1.0]</td>
<td>0.0 [0.0-0.0]</td>
<td></td>
</tr>
<tr>
<td>Sleep interference‡</td>
<td>Mean ± SD 2.2 ± 2.6</td>
<td>1.7 ± 2.5</td>
</tr>
<tr>
<td>Median [Q1-Q3] 1.0 [0.0-3.0]</td>
<td>1.0 [0.0-2.0]</td>
<td></td>
</tr>
<tr>
<td>Enjoyment of life interference‡</td>
<td>Mean ± SD 1.3 ± 1.6</td>
<td>1.5 ± 2.6</td>
</tr>
<tr>
<td>Median [Q1-Q3] 1.0 [0.0-2.0]</td>
<td>0.0 [0.0-2.0]</td>
<td></td>
</tr>
<tr>
<td>Worst pain ≥ 4, n (%)</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Worst pain ≥ 6, n (%)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; SD, standard deviation.
†Neuropathic pain, as defined by the Neuropathic Pain Questionnaire–Short Form.18
‡Assessed among patients reporting some amount of incisional pain.
§Defined as the average of questions 1 through 4 on the modified Brief Pain Inventory.
††Defined as the average of questions 5a through 5g on the modified Brief Pain Inventory.

Form.18
Many studies have shown that acute postoperative pain is associated strongly with persistent incisional pain, possibly because adequate analgesia blocks the initial pain stimulus, which is crucial for progression to chronic pain. But whether the relationship is causal remains unclear. As reported previously, IV acetaminophen reduced acute postoperative pain in the cardiac surgical patients of the study presented here. The reduction in pain score averaged about 1 point on a 0-to-10 NRS. The effect was small and may have been insufficient to block development of persistent pain. In addition, even though there are strong theoretical reasons to believe that acetaminophen might reduce the risk of persistent pain via various other mechanisms, this did not occur under the circumstances of the study presented here. The lack of association between acetaminophen and persistent pain in this study may have been due to the complex and multifactorial mechanisms involved in development of persistent pain after cardiac surgery, which perhaps requires multiple modalities to overcome.

The incidence of neuropathic pain was 10% at 30 days and healing period for a sternotomy. However, the prevalence remained 41% at 3 months, which was almost identical to the 40% reported by Choiniere et al \cite{19} and similar to the 49% incidence previously reported by the authors of the study presented here.

Among those reporting pain at 90 days, the pain intensity was low, averaging < 3 points on a 0-to-10 scale, which is consistent with what was reported previously about persistent poststernotomy pain being common, but rarely severe. As might be expected from relatively low pain intensity, the patients in the study presented here reported that persistent incisional pain only minimally interfered with life activities including mood, relationships, sleep, walking, work, and overall enjoyment.

In contrast to the authors' hypothesis, IV acetaminophen was not associated with lower persistent incisional pain at 3 months. The authors are aware of only a single previous study evaluating the effect of IV acetaminophen on persistent pain; Koyuncu et al \cite{10} randomly assigned abdominal hysterectomies to acetaminophen, 1 g, or placebo, every 6 hours for 72 hours. The incidence of pain at 3 months was reduced from 34% to 11% in patients given acetaminophen. Furthermore, the intensity of pain was decreased by acetaminophen. However, there were important differences between the trials by Koyuncu et al and the one presented here. Open hysterectomies are far less invasive than are sternotomies, cause less acute pain, involve no bone pain, and heal more quickly. Furthermore, the cardiac patients in the study presented here were given acetaminophen for only 1 day rather than for 3 full days, as in the hysterectomy study. A longer administration period may have benefited the patients of the study presented here, or perhaps the drug is simply more effective for smaller procedures.

Many studies have shown that acute postoperative pain is associated strongly with persistent incisional pain, possibly because adequate analgesia blocks the initial pain stimulus, which is crucial for progression to chronic pain. But whether the relationship is causal remains unclear. As reported previously, IV acetaminophen reduced acute postoperative pain in the cardiac surgical patients of the study presented here. The reduction in pain score averaged about 1 point on a 0-to-10 NRS. The effect was small and may have been insufficient to block development of persistent pain. In addition, even though there are strong theoretical reasons to believe that acetaminophen might reduce the risk of persistent pain via various other mechanisms, this did not occur under the circumstances of the study presented here. The lack of association between acetaminophen and persistent pain in this study may have been due to the complex and multifactorial mechanisms involved in development of persistent pain after cardiac surgery, which perhaps requires multiple modalities to overcome.

The incidence of neuropathic pain was 10% at 30 days and only a few of the patients reported neuropathic pain at

Table 4
Description of Incisional Pain at 90 Days After Surgery by Treatment Group
Among Patients Who Completed Follow-Up Assessments

<table>
<thead>
<tr>
<th>90-Day Assessment</th>
<th>IV Acetaminophen (n = 50)</th>
<th>Placebo (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients reporting any incisional pain, n (%)</td>
<td>20 (40)</td>
<td>23 (42)</td>
</tr>
<tr>
<td>Neuropathic incisional pain, n (%)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Overall incisional pain severity\[^{†}\] mean ± SD
- Mean | 1.0 ± 1.0
- Median [Q1-Q3] | 0.8 [0.0-1.5]

Worst pain in the past 24 h\[^{†}\]^\[^{‡}\]
- Mean ± SD | 2.0 ± 2.2
- Median [Q1-Q3] | 1.5 [0.0-3.0]

Least pain in the past 24 h\[^{†}\]^\[^{‡}\]
- Mean ± SD | 0.3 ± 0.6
- Median [Q1-Q3] | 0.0 [0.0-0.5]

Average pain in the past 24 h\[^{†}\]^\[^{‡}\]
- Mean ± SD | 1.2 ± 1.2
- Median [Q1-Q3] | 1.0 [0.0-2.0]

Current pain\[^{†}\]^\[^{‡}\]^\[^{‡}\]
- Mean ± SD | 0.4 ± 1.1
- Median [Q1-Q3] | 0.0 [0.0 to 0.0]

General activity interference\[^{†}\]^\[^{‡}\]^\[^{‡}\]
- Mean ± SD | 0.8 ± 0.9
- Median [Q1-Q3] | 0.6 [0.0 to 1.4]

Mood interference\[^{†}\]^\[^{‡}\]^\[^{‡}\]
- Mean ± SD | 1.4 ± 1.7
- Median [Q1-Q3] | 1.0 [0.0-2.5]

Walking ability interference\[^{†}\]^\[^{‡}\]^\[^{‡}\]
- Mean ± SD | 0.4 ± 0.6
- Median [Q1-Q3] | 0.0 [0.0-1.0]

Normal work interference\[^{†}\]^\[^{‡}\]^\[^{‡}\]
- Mean ± SD | 0.4 ± 1.4
- Median [Q1-Q3] | 1.0 [0.0-3.0]

Interference of relations with other people\[^{†}\]^\[^{‡}\]^\[^{‡}\]
- Mean ± SD | 0.3 ± 0.6
- Median [Q1-Q3] | 0.0 [0.0-0.5]

Sleep interference\[^{†}\]^\[^{‡}\]^\[^{‡}\]
- Mean ± SD | 1.2 ± 1.7
- Median [Q1-Q3] | 0.0 [0.0-2.0]

Enjoyment of life interference\[^{†}\]^\[^{‡}\]^\[^{‡}\]
- Mean ± SD | 0.5 ± 0.7
- Median [Q1-Q3] | 0.0 [0.0-1.0]

Abbreviations: IV, intravenous; SD, standard deviation.

\[^{‡}\]Assessed among patients reporting some amount of incisional pain.

\[^{†}\]Defined as the average of questions 1 through 4 on the modified Brief Pain Inventory.

\[^{‡}\]Defined as the average of questions 5a through 5g on the modified Brief Pain Inventory.
3 months. There was no apparent association between acetaminophen and neuropathic pain; however, the study had little power to evaluate this uncommon outcome. The results of the study presented here were consistent with those of recent studies, suggesting that the neuropathic component of persistent surgical pain may be lower than reported previously. Possibly, direct nerve injury is the primary etiology of persistent pain after cardiac surgery and could result from incomplete ossification, sternocostal chondritis, intrathoracic scar, or allergic reactions to pacing wires. However, it also is likely that formal quantitative testing done in a clinic would have identified more neuropathic pain than the validated questionnaire used for this study.

This study had several limitations. Primary outcome data were assessed based on phone calls, which may have resulted in inaccurate data due to confusion from medication, mental health state, or other disease. The study was underpowered to detect small differences in pain scores between groups at 30 and 90 days after surgery. If there was truly a small IV acetaminophen effect on pain, the study was not powered to detect it. This study also was limited by no follow-up for 35 patients (24%) at 30 days and for 42 patients (29%) at 90 days after surgery. It was assumed that patients were missing at random for the analyses, but it is possible that this was not the case. If follow-up patients were not missing at random (ie, if certain patient characteristics are associated with more loss to follow-up), it is possible that the results were confounded despite randomization. To account for this, the authors adjusted for measured baseline characteristics that were imbalanced between groups. However, the analyses potentially could be confounded by unmeasured patient characteristics. Because of these limitations, this study cannot be used to assess for causality and is more appropriate for hypothesis generation.

In summary, administration of IV acetaminophen for 24 hours reduced acute pain after cardiac surgery by about 1 point on a 0-to-10 NRS and was noninferior to opioid consumption. However, IV acetaminophen was not associated with lower intensity of incisional pain at 30 and 90 days. The incidence of persistent surgical pain at 90 days after cardiac surgery was substantial, at about 40%; among those reporting any pain, the intensity was low, averaging <3/10, and had minimal influence on life activities or overall enjoyment. Acetaminophen should not be used to decrease persistent surgical pain. The results suggest that mechanisms of persistent incisional pain are complex and multifactorial and that clinical approaches targeting multiple pathways may be needed to overcome this problem.

Appendix A. Supplementary Material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1053/j.jvca.2017.05.029.

References

12 Sinatra RS, Jahr JS, Reynolds LW, et al. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection...


