REVIEW ARTICLE

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Old Drug, New Route: A Systematic Review of Intravenous Acetaminophen After Adult Cardiac Surgery

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THE MANAGEMENT OF postoperative pain after cardiac surgery remains clinically challenging. Well-controlled pain is critical to maintaining the physical and psychologic well-being of each patient and can help facilitate timely extubation, comfortable breathing, and early postoperative ambulation. On the other hand, left poorly managed, postoperative pain can lead to rising catecholamine levels, ultimately triggering myocardial ischemia, stroke, or bleeding complications.[1-3] Insufficient pain control also can limit patient mobility, increasing the risk of deep vein thrombosis and pneumonia, in addition to the harmful psychologic consequences of insomnia and demoralization.[3,4] Ultimately, inadequate analgesia can escalate the cost of medical care, with longer stays in the hospital and a greater risk of hospital readmission.[1,4]

Opioids are the most common medications used to control the intense pain from sternotomy early after surgery.[5,6] Even though opioids are potent analgesics, undesirable side effects constitute major limitations, particularly when used in higher doses. Opioid therapy can lead to excessive sedation, confusion, respiratory depression, constipation, biliary spasm, and postoperative nausea and vomiting.[7,8] To limit the adverse effects without sacrificing adequate pain management, opioids often are administered in combination with acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) to provide both central and peripheral analgesia, a concept known as "multi-modal postoperative pain management."[9] Compared with opioids, NSAIDs are devoid of the deleterious effects on the central nervous system, exerting their analgesic effects by inhibiting cyclooxygenase enzymes and suppressing prostaglandin synthesis. Several studies have noted low complication rates associated with their short-term use when administered selectively after coronary artery bypass graft surgery (CABG).[10-12] However, concerns remain regarding the use of NSAIDs after cardiac surgery because of their association with renal impairment, gastrointestinal complications, and hemorrhage secondary to platelet dysfunction.[13] On the whole, NSAIDs have not been adopted widely for pain management after cardiac surgery because of concern for their potential side-effects and the presence of a Food and Drug Administration (FDA) black box label warning against their use immediately after CABG.[2,13,14]

Acetaminophen is a widely used analgesic and antipyretic that represents another nonopioid option for pain relief after cardiac surgery. In contrast to NSAIDs, acetaminophen has no anti-inflammatory activity and does not present unwanted platelet, kidney, or gastrointestinal side effects.[7,15-18] Known as paracetamol outside of North America, acetaminophen was first discovered in 1877, but it was not until 1950 that it was marketed for clinical use as a pain reliever.[18] While it is less potent in its analgesic properties, unlike opiates, acetaminophen has no respiratory depressant action and does not cause nausea or vomiting.[18,19] It has a minimal hemodynamic effect, and the only contraindications to its use are severe hepatic impairment, allergy, or hypersensitivity. Given its safety profile, it has become a common household drug and has been available in oral form without prescription since 1959.[18] To date, the mechanism of action of acetaminophen is not understood completely, although it is believed to involve inhibition of cyclooxygenase enzymes and prostaglandin synthesis in the central nervous system.[15,20-23] Acetaminophen also may block the origin of pain impulses peripherally by activating descending serotonergic pathways that suppress pain signal transmission in the spinal cord.[24,25]

With its distinct mechanisms of action, acetaminophen can be combined with centrally acting opiates to provide synergistic pain relief after cardiac surgery and limit opioid-induced side effects such as nausea and vomiting. Oral acetaminophen appears to be most applicable for analgesia several days after cardiac surgery, when it usually is administered in combination with an oral opioid, such as hydrocodone or oxycodone. However, oral acetaminophen appears to be less useful in the early perioperative setting because of slowed gastric emptying and enteral absorption in the first 24 hours after surgery, limiting its bioavailability, even if administered rectally.[26-29]

In recent years, acetaminophen has become available in an intravenous (IV) form, providing an opportunity for its use in the early postoperative period. The first IV acetaminophen option to become available clinically was propacetamol, a prodrug that becomes rapidly hydrolyzed to acetaminophen after injection in

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the blood. In use for approximately 20 years throughout Europe and Asia, the administration of propacetamol was limited by localized pain at the injection site and the development of contact dermatitis among healthcare professionals because the powdered drug requires reconstitution into solution before use.[30-32] A ready-to-use formulation of IV acetaminophen thereafter became available in 2001 under the trade name Perfalgan (Bristol-Myers Squibb, Anagni, Italy) in Europe and subsequently in 2010 in the United States under the trade name Ofirmev (Mallinckrodt Pharmaceuticals, St Louis, MO).

Intravenous acetaminophen has been promoted as a convenient, fast-acting, safe analgesic that is readily usable in the perioperative period, allowing the early initiation of multimodal analgesia.[33,34] The IV route enables the delivery of this drug during the immediate postoperative period, whereas acetaminophen via the oral or rectal route may be difficult or ineffective early after surgery due to low bioavailability.[28,35] After IV administration of acetaminophen, a rapid and high plasma concentration is achieved within 5 minutes, and pain relief occurs within a few minutes.[34] V-administered acetaminophen rapidly crosses the blood-brain barrier, and it is readily detectable in the cerebrospinal fluid (CSF) within minutes because of its high lipid solubility.[33,36] Compared with rectal or oral administration, IV acetaminophen leads to earlier and higher peak CSF concentration values with less variability.[37]

Given the interest in this promising new (and yet old) therapeutic modality, several studies have been performed to evaluate the potential benefits of IV acetaminophen when administered early after cardiac surgery, yielding mixed results. The objectives of this systematic review were to summarize the published studies to date and to determine the current role for perioperative IV acetaminophen after adult cardiac operations.

METHODS

A computerized literature search for abstracts was performed using the PubMed database and Cochrane Library from the earliest available date until June 2015. The initial key words and MESH terms were *propacetamol, intravenous acetaminophen, intravenous paracetamol, Perfalgan, Ofirmev, cardiac surgery, coronary artery bypass graft surgery,* and *heart valve replacement surgery*. Relevant manuscripts were reviewed, and the reference lists of each pertinent article were assessed for further identification of potentially appropriate studies. Original manuscripts and review articles focusing on the safety and efficacy of IV acetaminophen early after adult cardiac surgery were included for evaluation. No language restrictions were applied. Given the varied analgesic protocols and pain score results, a formal meta-analysis was not feasible. The primary outcomes of interest were postoperative pain scores and opioid consumption. Additional outcomes included pulmonary function and hemodynamic parameters and the incidence of postoperative nausea and vomiting. This systematic review was performed in keeping with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and the Cochrane approach to systematic reviews.

RESULTS

Nine articles published between 1999 and 2010 featuring the results of randomized clinical trials were selected for this review (Table 1). The first clinical study to evaluate the use of IV acetaminophen after cardiac surgery was a randomized clinical trial performed by Ranucci et al who compared the analgesic effects of ketorolac (60 mg IV), propacetamol (2 g IV, equivalent to 1 g of acetaminophen[32]), and tramadol (200 mg IV) for pain management among 60 patients undergoing cardiac surgery.[38] Patients were assigned randomly to receive 1 of the 3 analgesics, which were administered at the completion of the surgery. Once the patient arrived in the intensive care unit (ICU), he or she could receive 1 additional dose of the randomly assigned therapy, but no other background opioid therapy was provided. Patient pain intensity was assessed 6 hours after surgery, after patients already had been extubated. The authors found that compared with ketorolac and tramadol, pain control was significantly less effective with propacetamol based on a 5-item verbal pain score. A significantly greater number of patients in the propacetamol group reported persistent "severe pain" after surgery compared with the 2 other analgesic groups ($p < 0.05$). Moreover, patients in the propacetamol group more often required a second analgesic dose. Using the dose regimen applied in this study, the authors noted that propacetamol was the least effective analgesic.[38]

Because hypotension previously had been reported as a potential concern with acetaminophen administration,[43] and a small amount of mannitol is used in its IV preparation, Avellaneda et al performed a hemodynamic assessment of propacetamol after cardiac surgery.[39] The authors randomly assigned 72 patients after CABG or valve surgery to receive a single dose of ketorolac, metamizol, or propacetamol (1 g IV) early after extubation. Propacetamol was noted to decrease the cardiac index by 10% compared with the other agents ($p < 0.05$), but no vasodilatory effect was observed. All 3 agents led to a significant reduction in pain 60 minutes after administration. Even though pain was relieved the least with propacetamol compared with the other agents, the authors had administered a lower and potentially subtherapeutic dose of propacetamol to these patients (1 g instead of the usual 2 g).[39]

Lahtinen et al conducted the first randomized placebo-controlled trial to evaluate the use of IV acetaminophen after cardiac surgery.[7] Published in 2002, these authors randomly assigned 79 CABG patients to receive either placebo or propacetamol, 2 g IV (equivalent to 1 g of acetaminophen[32]) every 6 hours for 72 hours in addition to background oxycodone patient-controlled analgesia (PCA). The authors found that, compared with placebo, propacetamol treatment led to a nonsignificant (NS) 13% reduction in oxycodone consumption over the first 72 hours after surgery ($p = 0.15$). Propacetamol did not improve pain scores ($p =$ NS) or postoperative pulmonary function ($p =$ NS), and the incidence of postoperative nausea and vomiting was similar in the 2 groups ($p =$ NS). In a post hoc analysis, however, the authors noted a significant reduction in oxycodone consumption within the first 24 hours in the propacetamol group ($p = 0.04$). The authors concluded that propacetamol did not enhance opioid-based analgesia or significantly reduce cumulative opioid consumption as an adjunct to PCA-oxycodone after CABG.[7]

In the second placebo-controlled trial published on the subject, Khalil et al performed a controlled trial of 32 off-pump CABG patients, who were assigned randomly to receive

Table 1. Published Clinical Trials Evaluating the Use of Intravenous Acetaminophen After Adult Cardiac Surgery

Lead Author	Year	Study Type	Study Design	Outcomes	Key Findings	Study Limitations
Ranucci[38]	1999	Randomized clinical trial	Propacetamol 2 g IV (equivalent to 1 g acetaminophen[32]) (n = 20)	Patient pain scores	Propacetamol was the least effective analgesic	Only 1 to 2 doses of study medication given
			Ketorolac 60 mg IV (n = 20)		Propacetamol group more often required a second analgesic dose	Small patient groups
			Tramadol 200 mg IV (n = 20)		Rate of persistent "severe pain" highest in propacetamol group ($p < 0.05$)	
Avellaneda[39]	2000	Randomized clinical trial	Propacetomol 1 g IV (equivalent to 500 mg acetaminophen[32]) (n = 22)	Hemodynamic outcomes (blood pressure, cardiac index)	Propacetamol decreased cardiac index by 10% ($p < 0.05$)	Single dose of study medication
			Ketorolac 30 mg IV (n = 23)	Patient pain scores	No vasodilatory effect with propacetamol	
			Metamizol 2 g IV (n = 27)		Pain relief less marked with propacetamol	
Lahtinen[7]	2002	Randomized clinical trial	Propacetamol 2 g IV (equivalent to 1 g acetaminophen [32]) q6h for 72 hours (n = 40)	Oxycodone consumption	Nonsignificant 13% reduction in oxycodone consumption over the first 72 hours with propacetamol ($p = 0.15$)	PCA may have hindered ability to show benefit with IV propacetamol
			Placebo (n = 39)	Patient pain scores	No improvement in pain scores	
			On top of background IV oxycodone PCA	Pulmonary function	No improvement in postoperative pulmonary function	
				Nausea and vomiting	No reduction in nausea/vomiting	
					Post hoc analysis suggested reduction in oxycodone consumption within first 24 hours in the propacetamol group ($p = 0.04$)	
Khalil[40]	2005	Randomized clinical trial	Acetaminophen 1 g IV q6h for 24 hours (n = 17)	Patient pain scores	IV acetaminophen led to lower pain scores (at 6 and 12 hours, $p < 0.05$) and less sedation (at 12 and 18 hours, $p < 0.05$)	Small study
			Placebo IV q6h for 24 hours (n = 15)	Ramsay sedation scale	27% less morphine consumed with IV acetaminophen ($p < 0.05$)	Uncertain statistical methods
			On top of background IV PCA	Opioid consumption	Lower incidence of nausea ($p < 0.05$), but not vomiting	
				Nausea and vomiting		
Pettersson[26]	2005	Randomized clinical trial	Acetaminophen 1 g IV q6h for 24 hours (n = 39)	Opioid consumption	21% significant reduction in opioid consumption over the first 24 hours with IV acetaminophen ($p = 0.02$)	Background IV ketobemidone infusion for all patients may have hindered ability to show benefit of IV acetaminophen
			Acetaminophen 1 g PO q6h for 24 hours (n = 38)	Patient pain scores	No improvement in pain scores	
			On top of background IV ketobemidone infusion	Nausea and vomiting	No reduction in nausea/vomiting	
Pettersson[27]	2006	Randomized clinical trial	Acetaminophen 1 g IV q6h for 24 hours (n = 24)	Patient pain scores	No improvement in pain scores	Background IV ketobemidone infusion for all patients may have hindered ability to show benefit of IV acetaminophen

Table 1 (*continued*)

Lead Author	Year	Study Type	Study Design	Outcomes	Key Findings	Study Limitations
			Acetaminophen 1 g PR q6h for 24 hours (n = 24)	Plasma acetaminophen concentrations	Acetaminophen plasma concentration was 95 μmol/L after the first IV dose; IV acetaminophen gave rise to a fast and predictable plasma concentration	Small patient groups
			On top of background IV ketobemidone infusion		Concentration was only 1 μmol/L after first rectal dose; rectal administration resulted in a slow and unpredictable uptake	
Cattabriga[3]	2007	Randomized clinical trial	Acetaminophen 1 g IV q6h for 72 hours (n = 56)	Morphine consumption	Patients who received IV acetaminophen had significantly less pain at rest at the 12-, 18-, and 24-hour time points and less pain during deep breaths at the 12-hour mark (all $p < 0.01$).	Use of background of continuous IV tramadol may have hindered ability to illustrate IV acetaminophen benefits
			Placebo IV q6h for 72 hours (n = 57)	Patient pain scores	After 24 hours, the 2 groups did not differ in terms of pain at rest and deep breath	
			On top of background of continuous IV tramadol (300 mg per 24 hours) for 3 days and breakthrough IV morphine as needed	Nausea and vomiting	No significant difference in cumulative morphine consumption No difference in the rate of nausea and vomiting	
Eremenko[41]	2008	Randomized clinical trial	Acetaminophen 1 g IV q6h for 3 doses (n = 22)	Opioid consumption	Patients who received IV acetaminophen had 36% lower opioid requirements after CABG ($p = 0.02$)	Small study
			Placebo IV q6h for 3 doses (n = 23)	Patient pain scores	Acetaminophen patients had significantly less pain (81% lower pain intensity, $p = 0.01$) at the time of extubation	Uncommonly used opioid analgesic
			On top of background of intermittent IV opioid analgesia (trimeperidine)	Pulmonary function	39% greater inspiratory lung capacity ($p = 0.03$) for acetaminophen patients at extubation	
Atallah[42]	2010	Randomized clinical trial	Acetaminophen 1 g IV q6h for 4 doses (n = 30)	Morphine consumption	Patients who received IV acetaminophen required 62% less morphine after CABG ($p < 0.05$)	Small study
			Placebo IV q6h for 4 doses (n = 30)	Patient pain scores	Acetaminophen patients were extubated earlier ($p < 0.05$) and had significantly lower pain scores ($p < 0.05$)	
			On top of background intermittent IV morphine as needed	Extubation time PaO_2, $PaCO_2$ and plasma cortisol levels	Acetaminophen patients had higher PaO_2 and lower $PaCO_2$ and lower postoperative plasma cortisol levels	

Abbreviations: CABG, coronary artery bypass graft; IV, intravenous; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PCA, patient-controlled analgesia; PO, by mouth; PR, per rectum.

either placebo or IV acetaminophen, 1 g every 6 hours, for 24 hours after surgery in addition to a background of intravenous morphine PCA.[40] Patients who received acetaminophen had significantly lower pain scores (at 6 and 12 hours, $p < 0.05$) and less sedation, using the Ramsay sedation scale (at 12 and 18 hours, $p < 0.05$), early after surgery. Acetaminophen patients also required 27% less morphine in the first 24 hours ($p < 0.05$) and had a lower incidence of nausea ($p < 0.05$) after surgery (although the incidence of vomiting was the same). Plasma cortisol levels were similar in the 2 groups after surgery. The study was limited by its very small size and uncertain statistical analysis, which should have featured an analysis of variance instead of repeated between-group comparisons. In their conclusions, the authors noted that IV acetaminophen in addition to morphine PCA produced an opioid-sparing effect, with improved pain scores and less sedation, compared with morphine alone.[40]

Pettersson et al performed 2 randomized controlled trials to evaluate the role of IV acetaminophen after cardiac surgery.[26,27] In the first trial, they compared IV acetaminophen with oral acetaminophen in 77 CABG patients.[26] For 24 hours, patients received 1 g of acetaminophen via either the IV or oral route every 6 hours after extubation. All patients received a continuous IV infusion of the opioid ketobemidone at a rate of 1 mg/hour on arrival in the ICU after surgery, with additional boluses and an increased rate for worsening pain. In this study, the authors found that patients who received IV acetaminophen required fewer opioids during the 24-hour study period compared with oral acetaminophen ($p = 0.02$). However, pain scores and the incidence of nausea and vomiting did not differ between the groups ($p =$ NS). These results led the authors to conclude that compared with oral acetaminophen, the administration of IV acetaminophen yielded a limited opioid-sparing effect after CABG that was of questionable clinical benefit.[26]

Subsequently, Pettersson et al performed a second study to compare IV acetaminophen with rectal acetaminophen by measuring plasma concentrations after their administration to patients recovering from cardiac surgery.[27] The investigators randomly assigned 48 patients to receive either 1 g of IV acetaminophen or 1 g of rectal acetaminophen every 6 hours for 4 doses during the first 24 hours after CABG or aortic valve replacement. As in their earlier study, all patients received a continuous IV infusion of ketobemidone in the ICU after surgery. Blood samples were drawn before and every 20 minutes after the first and fourth acetaminophen doses. The authors reported the mean acetaminophen plasma concentration was 95 μmol/L after the first IV dose, whereas patients who were administered rectal acetaminophen had a concentration of only 1 μmol/L 20 minutes after the first dose. Rectal administration resulted in a slow and unpredictable uptake, with stable plasma concentrations noted only after 3 doses had been administered. On the other hand, IV acetaminophen gave rise to a fast and predictable plasma concentration within 40 minutes of administration. These data were congruent with previous noncardiac surgery investigations,[28,29,34-36] confirming the challenges associated with perioperative rectal acetaminophen administration and highlighting the utility of the IV route, at least initially, to reach an early effective plasma concentration.[27] Interestingly, however, despite the plasma concentration differences, pain scores did not differ between the IV and rectal patient groups ($p =$ NS).

Cattabriga et al performed the largest trial to date on the use of IV acetaminophen after cardiac surgery.[3] In their double-blind placebo-controlled study, patients were assigned randomly to receive either 1 g of IV acetaminophen ($n = 56$) every 6 hours for 72 hours total (starting 15 minutes before the end of surgery) or placebo ($n = 57$) in addition to a background of continuous IV tramadol (300 mg per 24 hours) for 3 days and breakthrough IV morphine as needed. The authors compared the outcomes of the 2 patient groups at several time points and applied Bonferroni correction to account for the multiple group comparisons. Cattabriga et al noted that patients who were assigned randomly to receive IV acetaminophen had significantly less pain at rest (assessed using the visual analog scale) at the 12-, 18-, and 24-hour time points compared with the placebo group; they also experienced less pain with deep breaths at the 12-hour mark (all $p < 0.01$). However, after 24 hours, the 2 groups did not differ in terms of pain at rest or deep breath. Patients treated with IV acetaminophen required less cumulative morphine in the trial, but this difference did not reach statistical significance ($p = 0.27$), and there was no difference in the rate of nausea and vomiting between the groups ($p =$ NS). Overall, the authors concluded that IV acetaminophen in combination with tramadol provided effective pain control, with the benefit most apparent in the first 24 hours after surgery.[3]

In another small placebo-controlled trial of 45 CABG patients, Eremenko et al randomly assigned 22 patients to receive 1 g of acetaminophen IV every 6 hours for 3 doses (starting 30 minutes before postoperative extubation), while 23 patients received placebo, on top of a background of intermittent IV opioid analgesia (trimeperidine).[42] In this study, patients who received IV acetaminophen required 36% fewer opioids after CABG ($p = 0.02$). At the time of extubation, acetaminophen patients also had an 81% reduction in pain intensity ($p = 0.01$) and experienced a 39% greater inspiratory lung capacity ($p = 0.03$) compared with patients who received placebo. With encouraging results, despite the small trial, the authors advocated for the routine use of IV acetaminophen as part of program of multimodal postoperative pain management early after cardiac surgery.[41]

In the final study published in the field, Atallah et al performed a controlled trial of 60 patients who had undergone valve replacement surgery.[42] Patients were assigned randomly to receive either IV acetaminophen ($n = 30$) 1 g every 6 hours for 4 doses (starting before sternum closure) or placebo ($n = 30$) in addition to a background of intermittent IV morphine as needed. The authors found that patients who received acetaminophen achieved extubation earlier after surgery ($p < 0.05$), had significantly lower pain scores ($p < 0.05$), and consumed 62% less morphine ($p < 0.05$) during the first 24 hours after surgery. Moreover, the authors noted that acetaminophen patients had higher P_aO_2 and lower P_aCO_2 levels, as well as lower postoperative plasma cortisol levels, compared to placebo patients. This led the authors to speculate that, through the reduction of morphine consumption and improved postoperative analgesia, IV acetaminophen may lead to less central respiratory depression and less postoperative stress after surgery.[42]

DISCUSSION

Pain control after cardiac surgery is a critical issue for patients and clinicians alike. Postoperative pain that is poorly managed can impede the cardiovascular, respiratory, and immune systems and ultimately increase the cost of medical care.[1,4] Sadly, pain that is inadequately controlled during the first postoperative week after CABG can predict the development of chronic, persistent pain in the subsequent months and years, with important consequences for long-term patient quality of life.[44] Even though opioids are the medications most commonly administered to alleviate postoperative pain, their use can be associated with challenging side effects, particularly when used in high doses early after cardiac surgery.[5-8]

As a method to limit opioid-induced side effects, acetaminophen can be combined with centrally acting opiates to provide synergistic pain relief after surgery, a concept known as "multimodal postoperative pain management."[9] Oral acetaminophen appeared to be less useful early after cardiac surgery due to limited bioavailability,[26-29] but recently acetaminophen has become available in an IV form, providing an opportunity for its use in the early postoperative period.

Several randomized studies have demonstrated that IV acetaminophen was safe and efficacious for the management of postoperative pain for patients undergoing noncardiac surgery (eg, abdominal and orthopedic surgeries). Significant adverse reactions associated with IV acetaminophen appeared to be extremely rare, occurring at an approximate incidence of fewer than 1/10,000.[45] IV acetaminophen reduced opioid requirements for patients recovering from noncardiac surgery[46-49] and decreased the incidence of postoperative nausea and vomiting, particularly when administered in a preemptive fashion before or during surgery.[50] In the most recent meta-analysis on the subject, Tzortzopoulou et al reviewed 36 studies involving 3,896 surgical patients, noting that 37% of patients who received a single dose of IV acetaminophen experienced effective postoperative analgesia for 4 hours compared with 16% who received placebo, yielding a number-needed-to-treat of 4.0 for benefit.[51] Acetaminophen also led to a 30% reduction in opioid consumption over 4 hours. However, this did not translate to a reduction in opioid-induced adverse events.[51]

In this systematic review, the authors summarized the literature to determine the current role for perioperative IV acetaminophen after adult cardiac surgeries. In all, 9 cardiac surgery trials were identified to date that have evaluated the use of IV acetaminophen. Even though all studies were randomized, only 1 was blinded, and all were designed as small pilot studies without prespecified outcomes or power (sample size) estimates. Each study varied in protocol design, duration of therapy, and use of background analgesia, precluding the ability to accurately summarize the published data in the form of a meta-analysis. Of note, no trial evaluated the potential benefits of preemptive analgesia with IV acetaminophen administration before cardiac surgery initiation.

Despite the exploratory nature of these studies and their limited sample sizes, several general conclusions can be made. When used without background opioid therapy, IV acetaminophen was not sufficient to control the intense pain that can occur after cardiac operations. In contrast, the sole use of ketorolac or tramadol may suffice as monotherapy for select patients.[38,39] Compared with the use of oral or rectal acetaminophen, IV acetaminophen therapy achieved higher plasma concentration levels and may reduce opioid consumption after surgery. However, IV acetaminophen did not actually improve postoperative pain scores compared with the oral or rectal routes of administration.[26,27] Among the trials comparing IV acetaminophen to placebo after cardiac surgery, conflicting results have been published. The 3 smallest placebo-controlled trials suggested that IV acetaminophen was associated with less opioid consumption, improved pain control, and improved pulmonary function early after surgery.[40-42] In contrast, the 2 largest clinical trials suggested that IV acetaminophen (on top of background or breakthrough opioid therapy) led to either no improvement in pain scores or a slight difference seen only during the first 24 hours, no significant reduction in opioid consumption, no improvement in pulmonary function, and no reduction in the incidence of nausea and vomiting after surgery as compared with placebo.[3,7] Of note, IV acetaminophen may decrease the cardiac index slightly after administration.[39]

Overall, the data published to date regarding the use of IV acetaminophen after cardiac surgery suggested a clinical benefit that was marginal at best. Ideally, in the future, a large, adequately powered, randomized trial will provide definitive data regarding the potential benefits of preoperative (preemptive) and postoperative IV acetaminophen administration after cardiac operations, with a focus on the analgesic and opioid-sparing properties of IV acetaminophen and its potential to improve postoperative pulmonary function. However, at present, the routine administration of IV acetaminophen to all adult patients recovering from cardiac surgery does not appear to be justified, given the data noted herein.

Recently, a perioperative pain guideline statement recommended the use of oral analgesics over IV administration, wherever possible, for patients who could use the oral route.[52] In keeping with this recommendation, the authors of this review believe the current role for IV acetaminophen after cardiac surgery should be limited only to select patient who are unable to tolerate oral analgesia during the first 24 to 48 postoperative hours and in situations in which opioids should be avoided, such as severe nausea or ileus. The authors of this review also favor its use among older patients for whom concerns may exist regarding excessive sedation, confusion, or aspiration, limiting the use of opioids and oral acetaminophen. One of the greatest benefits associated with IV acetaminophen is the rapid and predictable rise in plasma concentration minutes after its administration, especially when enteral absorption is limited early after surgery. As such, the authors of this review have used IV acetaminophen selectively for the management of fever in the initial few hours after surgery, although they limit its use to 1 or 2 doses, given its cost. The authors and others[38,39,41] have noted that IV acetaminophen usually did not provide sufficient analgesia when administered in isolation during the early postoperative period after cardiac operations.

In conclusion, acetaminophen achieves a higher plasma concentration when administered intravenously after cardiac surgery, but this does not necessarily improve postoperative pain scores compared with the oral or rectal route. IV acetaminophen was not sufficient for pain relief when used

as monotherapy after adult cardiac surgeries. Moreover, clinical trials in the cardiac surgery population have not reliably or consistently demonstrated benefit when IV acetaminophen was added to a background opioid therapy. As such, with minimal clinical benefit, the routine administration of IV acetaminophen to all adult cardiac surgery patients is not justified based on the data published to date. The authors suggest its use be limited to select patients after cardiac operations.

REFERENCES

1. Brennan F, Carr DB, Cousins M: Pain management: A fundamental human right. Anesth Analg 105:205-221, 2007
2. Mangano DT, Siliciano D, Hollenberg M, et al: Postoperative myocardial ischemia. Therapeutic trials using intensive analgesia following surgery. The Study of Perioperative Ischemia (SPI) Research Group. Anesthesiology 76:342-353, 1993
3. 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 32: 527-531, 2007
4. Apfelbaum JL, Chen C, Mehta SS, et al: Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 97:534-540, 2003
5. Searle NR, Roy M, Bergeron G, et al: Hydromorphone patient-controlled analgesia (PCA) after coronary artery bypass surgery. Can J Anaesth 41:198-205, 1994
6. Nay PG, Elliott SM, Harrop-Griffiths AW: Postoperative pain. Expectation and experience after coronary artery bypass grafting. Anaesthesia 51:741-743, 1996
7. Lahtinen P, Kokki H, Hendolin H, et al: Propacetamol as adjunctive treatment for postoperative pain after cardiac surgery. Anesth Analg 95:813-819, 2002
8. Wheeler M, Oderda GM, Ashburn MA, et al: Adverse events associated with postoperative opioid analgesia: A systematic review. J Pain 3:159-180, 2002
9. Kehlet H, Dahl JB: The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 77: 1048-1056, 1993
10. Kulik A, Ruel M, Bourke ME, et al: Postoperative naproxen after coronary artery bypass surgery: A double-blind randomized controlled trial. Eur J Cardiothorac Surg 26:694-700, 2004
11. Oliveri L, Jerzewski K, Kulik A: Black box warning: Is ketorolac safe for use after cardiac surgery? J Cardiothorac Vasc Anesth 28: 274-279, 2014
12. Engoren MC, Habib RH, Zacharias A, et al: Postoperative analgesia with ketorolac is associated with decreased mortality after isolated coronary artery bypass graft surgery in patients already receiving aspirin: A propensity-matched study. J Cardiothorac Vasc Anesth 21:820-826, 2007
13. Kulik A, Bykov K, Choudhry NK, et al: Non-steroidal anti-inflammatory drug administration after coronary artery bypass surgery: Utilization persists despite the boxed warning. Pharmacoepidemiol Drug Saf 24:647-653, 2015
14. Griffin M: Con: Nonsteroidal anti-inflammatory drugs should not be routinely administered for postoperative analgesia after cardiac surgery. J Cardiothorac Vasc Anesth 14:735-738, 2000
15. Flower RJ, Vane JR: Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). Nature 240:410-411, 1972
16. Niemi TT, Backman JT, Syrjala MT, et al: Platelet dysfunction after intravenous ketorolac or propacetamol. Acta Anaesthesiol Scand 44:69-74, 2000
17. Farquhar WB, Morgan AL, Zambraski EJ, et al: Effects of acetaminophen and ibuprofen on renal function in the stressed kidney. J Appl Physiol (1985) 86:598-604, 1999
18. Bertolini A, Ferrari A, Ottani A, et al: Paracetamol: New vistas of an old drug. CNS Drug Rev 12:250-275, 2006
19. Hynes D, McCarroll M, Hiesse-Provost O: Analgesic efficacy of parenteral paracetamol (propacetamol) and diclofenac in post-operative orthopaedic pain. Acta Anaesthesiol Scand 50:374-381, 2006
20. Hinz B, Cheremina O, Brune K: Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J 22: 383-390, 2008
21. Koppert W, Wehrfritz A, Korber N, et al: The cyclooxygenase isozyme inhibitors parecoxib and paracetamol reduce central hyperalgesia in humans. Pain 108:148-153, 2004
22. Piletta P, Porchet HC, Dayer P: Central analgesic effect of acetaminophen but not of aspirin. Clin Pharmacol Ther 49:350-354, 1991
23. Bonnefont J, Courade JP, Alloui A, et al: [Antinociceptive mechanism of action of paracetamol]. Drugs 63 Spec No 2:1-4, 2003
24. Pickering G, Loriot MA, Libert F, et al: Analgesic effect of acetaminophen in humans: First evidence of a central serotonergic mechanism. Clin Pharmacol Ther 79:371-378, 2006
25. Graham GG, Scott KF: Mechanism of action of paracetamol. Am J Ther 12:46-55, 2005
26. Pettersson PH, Jakobsson J, Owall A: Intravenous acetaminophen reduced the use of opioids compared with oral administration after coronary artery bypass grafting. J Cardiothorac Vasc Anesth 19: 306-309, 2005
27. Pettersson PH, Jakobsson J, Owall A: Plasma concentrations following repeated rectal or intravenous administration of paracetamol after heart surgery. Acta Anaesthesiol Scand 50:673-677, 2006
28. Schuitmaker M, Anderson BJ, Holford NH, et al: Pharmacokinetics of paracetamol in adults after cardiac operations. Anaesth Intensive Care 27:615-622, 1999
29. Goldhill DR, Whelpton R, Winyard JA, et al: Gastric emptying in patients the day after cardiac surgery. Anaesthesia 50:122-125, 1995
30. Sinatra RS, Jahr JS, Reynolds LW, et al: Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. Anesthesiology 102:822-831, 2005
31. Moller PL, Juhl GI, Payen-Champenois C, et al: Intravenous acetaminophen (paracetamol): Comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. Anesth Analg 101:90-96, 2005
32. Flouvat B, Leneveu A, Fitoussi S, et al: Bioequivalence study comparing a new paracetamol solution for injection and propacetamol after single intravenous infusion in healthy subjects. Int J Clin Pharmacol Ther 42:50-57, 2004
33. Jahr JS, Lee VK: Intravenous acetaminophen. Anesthesiol Clin 28:619-645, 2010
34. Moller PL, Sindet-Pedersen S, Petersen CT, et al: Onset of acetaminophen analgesia: Comparison of oral and intravenous routes after third molar surgery. Br J Anaesth 94:642-648, 2005
35. Hein A, Jakobsson J, Ryberg G: Paracetamol 1 g given rectally at the end of minor gynaecological surgery is not efficacious in reducing postoperative pain. Acta Anaesthesiol Scand 43:248-251, 1999
36. Bannwarth B, Netter P, Lapicque F, et al: Plasma and cerebrospinal fluid concentrations of paracetamol after a single intravenous dose of propacetamol. Br J Clin Pharmacol 34:79-81, 1992
37. Singla NK, Parulan C, Samson R, et al: Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen. Pain Pract 12: 523-532, 2012

38. Ranucci M, Cazzaniga A, Soro G, et al: Postoperative analgesia for early extubation after cardiac surgery. A prospective, randomized trial. Minerva Anestesiol 65:859-865, 1999

39. Avellaneda C, Gomez A, Martos F, et al: The effect of a single intravenous dose of metamizol 2 g, ketorolac 30 mg and propacetamol 1 g on haemodynamic parameters and postoperative pain after heart surgery. Eur J Anaesthesiol 17:85-90, 2000

40. Khalil AR, Hanafy MA, El-istekawy EM: The use of injectable paracetamol as an adjunct for postoperative pain management after off-pump fast-track coronary artery bypass grafting surgery. J Egyp Soc Cardiothorac Surg 13:25-33, 2005

41. Eremenko AA, Kuslieva EV: [Analgesic and opioid-sparing effects of intravenous paracetamol in the early period after aortocoronary bypass surgery]. Anesteziol Reanimatol Sep-Oct :11-14, 2008

42. Atallah MM, El-Gamal GA, Mageed NA, et al: The efficacy of perioperative intravenous paracetamol in valve replacement. EJIC 15: 17-25, 2010

43. Brown G: Acetaminophen-induced hypotension. Heart Lung 25: 137-140, 1996

44. Choiniere M, Watt-Watson J, Victor JC, et al: Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: A 2-year prospective multicentre study. CMAJ 186:E213-E223, 2014

45. Duggan ST, Scott LJ: Intravenous paracetamol (acetaminophen). Drugs 69:101-113, 2009

46. Peduto VA, Ballabio M, Stefanini S: Efficacy of propacetamol in the treatment of postoperative pain. Morphine-sparing effect in orthopedic surgery. Italian Collaborative Group on Propacetamol. Acta Anaesthesiol Scand 42:293-298, 1998

47. Hernandez-Palazon J, Tortosa JA, Martinez-Lage JF, et al: Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery. Anesth Analg 92:1473-1476, 2001

48. Aubrun F, Kalfon F, Mottet P, et al: Adjunctive analgesia with intravenous propacetamol does not reduce morphine-related adverse effects. Br J Anaesth 90:314-319, 2003

49. Macario A, Royal MA: A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. Pain Pract 11:290-296, 2011

50. Apfel CC, Turan A, Souza K, et al: Intravenous acetaminophen reduces postoperative nausea and vomiting: A systematic review and meta-analysis. Pain 154:677-689, 2013

51. Tzortzopoulou A, McNicol ED, Cepeda MS, et al: Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. Cochrane Database Syst Rev :CD007126, 2011

52. Chou R, Gordon DB, de Leon-Casasola OA, et al: Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 17: 131-157, 2016