Review Article

Clinical Implementation of A Multimodal Analgesia Regimen for Cardiac Surgical Patients

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ABSTRACT

Aim of review: Enhanced recovery after surgery (ERAS) protocols that utilize a multimodal, narcotic-sparing approach to pain management have proven to be effective for colorectal and other surgical subspecialties. However, perioperative pain management for cardiac surgical patients remain suboptimal and based primarily on the use of narcotic analgesics that expose patients to potential short- and long-term complications of opioid therapy. The objective of this investigation was to review the existing clinical evidence on the safety and efficacy of non-narcotic analgesics for the treatment of postoperative pain to create and implement a perioperative multimodal analgesic regimen that can be integrated into the current pain management practices for patients undergoing cardiothoracic operations.

Methods: A multidisciplinary task force consisting of anesthesiologists, surgeons, nurses, physician assistants, and pharmacists from the cardiovascular health service line was appointed to develop a standard order set in the electronic health record for the treatment of postoperative pain in patients undergoing cardiac operations. The PubMed and Cochrane databases were searched for studies on perioperative pain management after cardiac surgery. The available data were reviewed for quality and relevance to the management of cardiac surgical patients. Once consensus was achieved, an order set was created and universally applied for all cardiac surgical patients admitted to the surgical cardiovascular intensive care unit after the operation.

Recent findings: Evidence exists to support the safety and efficacy of a multimodal pain management protocol for cardiac surgical patients in an effort to improve patient satisfaction and comfort while limiting the adverse effects of opioid analgesics.

Summary: A multidisciplinary task force achieved consensus in creating an evidence-based, opioid-sparing, multi-modal medication order set for the management of postoperative pain in cardiac surgical patients. The standardized analgesic regimen was compliant with guidelines of The Joint Commission, widely accepted and quickly adopted in clinical use. Continuing investigations will be directed at quantifying whether the multimodal analgesic regimen will improve patient satisfaction, decrease postoperative pain scores, and reduce the incidence of opioid-related adverse events.

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Cardiothoracic surgery requires extensive soft tissue dissection, a sternotomy, and prolonged retraction that can produce significant postoperative pain. Adequate pain control is often challenging due to the extent of surgical trauma with the treatment and maintenance of circulatory function remaining a primary concern. Therefore, a narcotic-based anesthetic is typically administered for the operation, and patients are kept sedated on mechanical ventilator support at the time of admission to the surgical cardiovascular intensive care unit (CVICU). In addition, cardiac surgical patients are often elderly and at increased risk for postoperative bleeding, myocardial infarction, acute kidney injury, respiratory failure, stroke, delirium, and neurocognitive dysfunction. Effective and appropriate postoperative pain control can improve patient comfort, patient satisfaction, facilitate early mobilization, prevent respiratory complications and even decrease the incidence and severity of postoperative delirium. Furthermore, appropriate postoperative pain management might also decrease CVICU and hospital length of stay, prevent readmissions, decrease the risk of opioid dependence, and reduce pharmacy and hospital costs. Currently, there is no consensus for a universal evidence-based multimodal regimen for postoperative pain management in cardiac surgical patients. Clinical postoperative analgesic protocols vary widely and are often institution or even provider specific.

Traditionally, the treatment of postoperative pain in cardiac surgical patients relied heavily on intravenous (IV) or oral (PO) opioids. In response to the growing opioid epidemic in the United States, concern within the medical community as well as among the general public regarding the potential adverse effects of opioids, and the risk of opioid dependence, there has been increased interest in incorporating other drug families to develop a multi-modal approach for the routine treatment of postoperative pain (1,2). The move towards a value-based payment structure and the application of evidence-based practices with a greater emphasis on patient engagement and patient satisfaction also reinforce the need for continuous evaluation and improvement of current approaches to ensure patient comfort and safety while decreasing hospital length of stay and readmission rates.

The clinical application of enhanced recovery after surgery (ERAS) protocols have shown that moving away from opioid-heavy pain treatment protocols towards a multimodal pain management approach can have significant effects on patient comfort and overall recovery after surgery and decrease hospital length of stay (3). Although ERAS was initially applied in patients undergoing colorectal surgery, it has since been expanded and found to be effective for patients undergoing gynecological, orthopedic, and other operations within the general surgery subspecialties (4, 5).

Evidence from clinical investigations is available on the efficacy and safety of specific medications for the treatment of postoperative pain among cardiac surgical patients. However, there is limited clinical experience on the safety and efficacy of an integrated, multimodal analgesic regimen for the routine treatment of postoperative pain after cardiac operations. The purpose of this investigation was to systematically review the available published evidence to generate consensus among a multidisciplinary group of healthcare providers to create and implement a standardized multimodal analgesic regiment that can be clinically implemented for the management of the postoperative patient in cardiac surgical patients.

Methods

A task force to develop and implement evidence- and value-based care pathways was formed within the cardiovascular health service line of the hospital as part of a hospital-wide initiative to standardize patient care, improve patient satisfaction, and decrease cost. A subgroup within the task force was assigned to address the management of postoperative pain among cardiac surgical patients because rapid growth in clinical volume was associated with an escalation in the overall use of opioids and IV acetaminophen without corresponding improvements in patient satisfaction surveys. The objective of the cardiac surgical perioperative pain task force was to compile and review the available published evidence on pain management in cardiac surgery and develop a standardized comprehensive multimodal analgesic protocol for the treatment of

Table 1. Postoperative Pain Regimen.

	Drug	Dose	Frequency	Additional instructions
Standing	Gabapentin	CrCl > 60: 300 mg	TID	If pain persists, titrate as tolerated over 2-3 days.
		CrCl > 15 but < 60: 100 mg	TID	
		CrCl < 15 & HD: 100 mg	QD	
	Acetaminophen	1,000 mg	Q6 hr	
		Liver dysfunction: 500 mg	Q6 hr	
Pain mild	Ibuprofen	CrCl > 60: 400 mg	Q6 hr, prn	For a maximum of 72 hr.
		CrCl > 30 & < 60 or age > 65: 200 mg	Q6 hr, prn	Avoid use with dual antiplatelet therapy.
	Oxycodone	2.5 mg	Q3 hr, prn	Avoid use in CrCl < 30.
	Ketorolac, IV†	15 mg	Q6 hr, prn	For a maximum of 72 hr. Avoid use with dual antiplatelet therapy. Avoid use in CrCl < 30.
Pain moderate	Oxycodone	5 mg	Q3 hr, prn	
	Hydromorphone, IV†	0.2 mg	Q2 hr, prn	
	Ketorolac, IV†	CrCl > 60: 30 mg	Q6 hr, prn	For a maximum of 72 hr.
		CrCl > 30 & < 60 OR age > 65: 15 mg	Q6 hr, prn	Avoid use with dual antiplatelet therapy. Avoid use in CrCl < 30.
Pain severe	Oxycodone	10 mg	Q3 hr, prn	
	Hydromorphone, IV†	0.5 mg	Q2 hr, prn	
	Ketamine, IV†	0.25 mg/kg	Q2 hr, prn	Use with caution or dose reduce in renal or hepatic deficiency.
Refractory/ chronic pain	Lidocaine 1%, IV	1 mg/kg/hr	Cont inf	Check lidocaine level in bypass patients prior to initiation. Check lidocaine levels Q8 hrs (goal 3-5). Consult pain service.
	Ketamine, IV	0.1 mg/kg/hr	Cont inf	Consult pain service.
	Hydromorphone, IV	PCA		

CrCl, creatinine clearance in ml/min; TID, three times daily; HD, hemodialysis; QD, daily; Q, every; hr, hour; prn, as needed; IV, intravenous; Cont inf, continuous infusion; PCA, patient controlled analgesia.
*Select only 1 enteral and 1 intravenous medication; †Only use if enteral route is unavailable. Otherwise give enteral pain medication.
Tylenol(R) [package insert]. Fort Washington, PA: McNeil Consumer Healthcare Division: 2017.
Gabapentin [package insert]. Jacksonville, FL: Ranbaxy Pharmaceuticals Inc; 2014.
Hydromorphone hcl [package insert]. Lake Forest, IL: Hospira, Inc; 2018.
Motrin(R) [package insert]. New York, NY: Pfizer; 2006.
Ketalar(R) [package insert]. Spring Valley, NY: Par Pharmaceutical Companies, Inc; 2014.
Toradol(R) [package insert]. Ontario, Canada: Methapharm Inc; 2015.
Xylocaine(R) [package insert]. Zanesville, OH: Cardinal Health; 2018.
Oxycodone hcl [package insert]. Jacksonville, FL: Ranbaxy Pharmaceuticals; 2015.

postoperative pain in cardiac surgical patients admitted to the CVICU. The primary goals were to reduce opioid and IV acetaminophen use while improving patient satisfaction.

The cardiac surgery perioperative pain task force was comprised of representatives from the departments of anesthesiology, cardiothoracic surgery, nursing, and pharmacy. A pharmacist and anesthesiologist conducted a PubMed and Cochrane database literature search on the treatment of postoperative pain in cardiac surgical patients. Monthly meetings were held to review,

supplement, and discuss the available published literature. The evidence was evaluated based on the quality of the investigations, its applicability to cardiac surgical patients, and potential safety concerns. A final protocol was developed based on the available evidence and the expert opinion of task force members. Once a consensus was reached, the protocol (Tables 1 and 2) was presented and circulated to the other members of the department of anesthesiology, cardiothoracic surgery and CVICU staff for additional comments and suggestions prior to drafting a final

protocol for approval. A standard order set that was compliant with the The Joint Commission guidelines was then created based on the protocol and integrated into the postoperative orders for cardiac surgical patients within the electronic medical record. A feature within the order set permitted providers to override specific standardized orders and enter individualized prescriptions or make case-specific changes for individual patients when deemed necessary.

Recent Findings Based on the Published Literature

Opioids

Opioids are a group of endogenous, naturally occurring and synthetic drugs that target mu, delta and kappa receptors, with mu receptors being the primary site of action producing analgesia. Most opioids are available in multiple preparations that can be administered both orally and intravenously over large dose ranges. The opioids have been studied extensively with a vast number of reports describing both their efficacy and risks of adverse effects. To date, intravenous opioids continue to be the most commonly prescribed medication to treat postoperative pain. In addition to widespread availability, different opioid subclasses with a range of pharmacokinetic properties can be administered in combination to provide pain control with different onset-times and durations, thereby enabling the treatment of acute breakthrough pain while providing baseline pain control. However, opioids come with significant risks. Side effects range from ileus, nausea and vomiting to respiratory depression and delirium, which can significantly prolong the patient's ICU and hospital stay (6). Furthermore, long-term opioid use can lead to dependence and addiction. The worsening opioid epidemic in the United States has increased public awareness of the real and potential side effects, complications, and costs associated with opioids (1, 2). This problem puts pressure on healthcare providers to responsibly limit opioid use while still providing adequate pain control. According to the U.S. Department of Health and Human Services (HHS), "deaths involving opioid analgesics nearly quadrupled" from 1999 to 2013, and 37% of all the deaths due to drug overdoses involved prescription opioids (7,8). In addition, the number of deaths due to heroin abuse has increased by 39% from 2012 to 2013 (7). As a result, the HHS launched an initiative in 2015 to educate healthcare workers who prescribe opioid analgesics as well as address the potential for misuse and abuse of opioids by patients (8). As part of this initiative, the Centers for Medicare and Medicaid Services (CMS) published an executive summary of their "Opioid Misuse Strategy of 2016" in January 2017, outlining four priorities to combat this worsening crisis (9). Included in the priorities is a call for more evidence-based practices when managing acute and chronic pain and applying person-center and population-based tactics to decrease the risk of opioid misuse and overdose (9). To comply with these new strategies, healthcare providers have been urged to reassess current practices that rely primarily on the use of opioid analgesics for the management of perioperative pain.

Non-Steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenases (COX) that are involved in prostaglandin (PG) production. NSAIDs exert anti-inflammatory and analgesic actions through COX-2 inhibition, but also increase the risk of gastrointestinal bleeding by decreasing protective prostaglandins in the gastric mucosa through COX-1 inhibition. The bleeding risk involving other organ systems continues to be controversial and poorly understood, requiring more data to make accurate conclusions (10, 11). In addition, an estimated 1% - 5% of patients exposed to NSAIDs may develop nephrotoxic syndromes. While most cases of NSAID-induced acute kidney injuries are generally reversible, this side effect remains a significant concern among patients with chronic kidney disease or reduced renal perfusion (12,13). Selective COX-2 inhibitors were developed to provide anti-inflammatory actions while avoiding some of the undesired side-effects of COX-1 inhibition. However, in 2005, Nussmeier et al. published data showing that two COX-2 inhibitors were associated with an increased incidence of cardiovascular events (14). The mechanism is likely due to inhibition of prostacyclin (PGI2), which

is responsible for platelet inhibition. In the absence of PGI2, platelets have a higher propensity to interact with the blood vessel wall resulting in platelet aggregation and blood clot formation (15). Thus, the Food and Drug Administration issued a black box warning for use of NSAIDs in patients undergoing cardiac surgery. The American College of Cardiology Foundation and the American Heart Association subsequently stated in their 2011 practice guidelines that "COX-2 inhibitors are not recommended for pain relief in the postoperative period after CABG" (16). However, subsequent data have questioned the ability to extrapolate these outcomes to all NSAIDs and all patients undergoing cardiac operations (17). Both the PRECISION and SCOT trials showed similar cardiac complication rates for celecoxib and non-selective NSAIDs (18,19). However, as noted by Grosser et al., several limitations of the trials make it challenging to accurately interpret the results. For example, Grosser et al. pointed out that the doses for non-selective NSAIDs were at the higher end of the dosing range, while that of celecoxib was at the lower end. In addition, the conclusions in the SCOT trial were based on the intention-to-treat analysis and did not take into consideration the higher number of withdrawals from the COX-2 arm of the study (20).

Oliveri et al. conducted a retrospective observational study to determine the safety of ketorolac, a non-selective COX inhibitor, in cardiac surgery patients (17). They found that patients treated with ketorolac had similar or better outcomes with regards to gastrointestinal bleeding, perioperative MI, stroke and death. The authors reported that patients who had been treated with ketorolac were younger, had better baseline renal function and had undergone less complex operations. However, to address this selection bias, they compared their outcome data with expected outcomes based on Society of Thoracic Surgery risk assessment (17).

Gabapentin

Gabapentin is chemically related to and increases the neurotransmitter, gamma-aminobutyric acid (GABA). In the brain, GABA plays a significant role in both tonic inhibitory control and fast inhibitory synaptic transmission within the

Table 2. Preoperative and Intraoperative Pain Regimen.			
	Drug	Dose	Frequency
Preoperative	Acetaminophen	1000 mg	Once
		Liver dysfunction: 500 mg	Once
Intraoperative	Fentanyl, IV	10-50 µg/kg	
	Ketamine, IV	0.5 mg/kg	

IV, intravenous.

brain (21, 22). The mechanism of action behind gabapentin's analgesic effects is largely unknown. In animal models, it was found that the drug prevented allodynia and hyperalgesia (Abbott Laboratories, 2011)(23). In rat models, gabapentin administration binds to the a2δ subunit of voltage-gated calcium channels and decreased currents in spinal cord dorsal root ganglia neurons that may decrease neurotransmitter release by sensory neurons (24).

Published studies investigating the use of gabapentin for the treatment of postoperative pain in the setting of cardiothoracic surgery is limited and findings on benefits and adverse effects have been mixed.

In 2010, Menda et al. explored the effects of a single 600 mg oral dose of gabapentin 2 hours prior to coronary artery bypass graft surgery (CABG) on total morphine consumption. The authors found that gabapentin significantly decreased total morphine consumption compared to placebo. Secondary endpoints suggested gabapentin significantly decreased pain scores and the incidence of nausea. The number of over-sedated patients (Ramsay score >2) at hours 2, 6, and 12 were significantly higher in the gabapentin group compared to the placebo group. In addition, the duration of postoperative mechanical ventilator support was slightly but significantly prolonged in the gabapentin group compared to the placebo group (25).

In 2010, Rapchuk and colleagues studied whether perioperative administration of gabapentin versus placebo decreased the amount of fentanyl consumed by patient-controlled analgesia (PCA) in the first 48 hours after operation. On the day of operation, patients were randomized to either receive gabapentin 1.2 g or placebo approximately 2 hours prior to surgical incision. Postoperatively, patients were administered

either gabapentin 600 mg twice daily or matched placebo for 2 days. The authors found that the PCA fentanyl usage between the gabapentin and placebo arms did not differ significantly. Secondary endpoints such as time under anesthesia, time on cardiopulmonary bypass (CPB), time to extubation, sleep scores, number of antiemetics given in the first 48 hours, and adjunctive pain medications used were also not significantly different. Visual analog scale (VAS) scores and incidence of adverse events were also not significantly different in the study (26).

In 2011, Ucak and colleagues looked at the effects of gabapentin 1.2 g administered orally 1 hour prior to the procedure and 1.2 g per day for two days postoperatively on both acute and chronic pain. Postoperative pain scores at 1, 2, and 3 days were found to be lower in the gabapentin arm versus placebo (P < 0.05). Pain scores at 1 and 3 months did not differ statistically between the gabapentin and placebo groups (P > 0.05). Secondary outcomes showed that the requirement for intravenous tramadol as a rescue analgesic within 24 hours after extubation was decreased significantly in the gabapentin group compared to the placebo. There were no differences in the incidence of adverse effects and time to extubation between the two arms (27).

Existing evidence suggests that gabapentin may be effective when administered with opioid analgesics for the treatment of postoperative pain in cardiac surgical patients. Gabapentin has been demonstrated to decrease the severity of pain and in some studies, decrease opioid requirements. Oversedation is the predominant side effect of gabapentin and its administration prior to operation may increase the duration of postoperative ventilator support.

Ketamine

Ketamine produces both dissociative and analgesic effects through noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonism. Its amnestic and analgesic actions are not associated with significant cardiac or hemodynamic depression or the suppression of respiratory drive. Ketamine is often administered in subtherapeutic doses as an adjunct to general anesthesia for both cardiac and non-cardiac operations, but is rarely administered in the postoperative period as a sedative or to treat pain. The dose-dependent dissociative properties of ketamine have generated concerns about its potential to contribute to postoperative delirium. In addition, ketamine is often restricted for use as an anesthetic agent making it difficult to prescribe outside of the operating room. Finally, there are limited published studies investigating the use of ketamine administered in a scheduled dosing regimen or as an intravenous infusion for the treatment of postoperative pain.

Ketamine administered intraoperatively as an anesthetic adjunct has been found to both reduce the inflammatory cytokine response that is associated with cardiopulmonary bypass and to enhance the production of anti-inflammatory cytokines after major surgery (28). Hudetz et al. found that cardiac surgical patients who received ketamine 0.5 mg/kg IV as part of the induction of general anesthesia had significantly lower postoperative C-reactive protein concentrations when compared to placebo (odds ratio = 12.6; 95% confidence interval, 1.5-107.5; logistic regression). In addition, ketamine administered during anesthetic induction was associated with a significantly lower incidence of postoperative delirium compared to the patients who received placebo. The odds of developing postoperative delirium was approximately 13 times greater in the placebo group (29).

Postoperative ketamine use was studied by Nesher and colleagues in patients undergoing anterolateral thoracotomy for minimally invasive direct coronary artery bypass (MIDCAB), lung tumor resection, or median sternotomy for off-pump coronary artery bypass graft. The protocol randomized patients into a group that received morphine 1.5 mg bolus only (MO) or a group that received morphine 1 mg together with ketamine 5 mg (MK) via intravenous patient-controlled analgesia (IV-PCA). Each IV-PCA set up included a 7-minute lockout time. If pain was not attenuated within 30 minutes of initial IV-PCA activation, a rescue dose of diclofenac was made available. The MO group utilized twice the morphine compared to the MK group. In the postoperative period at 36 hours after the initiation of IV-PCA, 10 patients in the MO group still required IV-PCA compared to only 5 patients in the MK group (P < 0.05). Seventy

percent more diclofenac was utilized in the MO group. Pain intensity measured by visual analog scale (VAS) at 72-h follow up was significantly less in the MK group compared to the MO group (P = 0.03). In addition, subjectively rated wakefulness scores were significantly better in the MK group compared to the MO group (P = 0.014). Heart rate and systolic and diastolic blood pressures were similar while the respiratory rate and SpO2 were higher in the MK group (P = 0.001). No ketamine specific adverse effects were reported (30).

Lahtinen and colleagues evaluated ketamine for pain management after sternotomy. Patients scheduled for CABG received 75 μg/kg ketamine bolus followed by continuous infusion of ketamine 1.25 μg/kg/min or placebo for 48 hours after arrival to the postanesthesia care unit (PACU). The primary endpoint was oxycodone consumption from an IV-PCA device at 48 h after surgery. Oxycodone consumption in the ketamine group was significantly less than the placebo group. Secondarily, more patients in the ketamine group were very satisfied with their analgesic management (26 out of 44 or 59%) compared to patients in the placebo group (16 out of 46 or 35%; P=0.032). Secondary endpoints demonstrated no difference in VAS pain scores, tracheal extubation time, sedation scores, or cognitive function. Postoperative Paco2 remained within safe limits in both arms. Four patients in the ketamine group developed psychotomimetic disturbances compared to none in the placebo group (31).

Acetaminophen

One of the most commonly utilized non-opioid analgesics is acetaminophen because of its proven safety profile with few adverse effects. Acetaminophen is also generally well tolerated in critically ill patients with few contraindications and is available in preparations that permit administration by multiple routes that include rectal, oral and IV. The American Society of Anesthesiologists has recommended the use of acetaminophen as a first-line agent to be administered around-the-clock in a stepwise multimodal approach to the treatment of postoperative pain (32). Although incompletely understood, acetaminophen is thought to exert its analgesic action by inhibiting the synthesis of prostaglandins in the central nervous system (specifically COX-2) (33). The IV preparation of acetaminophen has an average wholesale price (AWP) in excess of $45 USD for a 1000 mg dose, which is substantially more than the oral preparations. The high cost of IV acetaminophen raises questions about its inherent and incremental value for the routine management of postoperative pain. Therefore, its availability for widespread use is often restricted at many institutions (33).

The published evidence as of 2016 supports the positive benefits of acetaminophen for the treatment of postoperative pain in cardiac surgery patients. In a randomized, placebo-controlled trial, Mamoun and colleagues evaluated the efficacy of IV acetaminophen in cardiac surgical patients. Patients were randomized to receive either acetaminophen 1 g IV every 6 hours for 24 hours or placebo starting after sternal closure. Acetaminophen was non-inferior to placebo for opioid consumption with an estimated ratio of means in opioid consumption of 0.89 (90% CI, 0.73-1.10; P = 0.28), but it was superior to placebo on mean pain intensity scores with an estimated difference in mean pain of -0.90 (95% CI, -1.39, -0.42; P < 0.001). There was no difference in postoperative nausea and vomiting, duration of mechanical ventilation, or ICU or hospital length of stay (34).

Jelacic et al. evaluated IV administration of acetaminophen as an adjunct analgesic in cardiac surgery with the primary endpoint of 24-hour opioid (in morphine equivalents) consumption. Patients received either placebo or acetaminophen 1000 mg IV immediately after anesthesia induction but prior to incision and again at the end of operation. Four additional doses were administered in the ICU starting 6 hours after admission. The acetaminophen arm consumed significantly fewer opioids compared to the placebo arm resulting in a 27% reduction in opioid consumption. Notably, significantly more patients in the acetaminophen group responded "very much" and "extremely well" when questioned about how their overall pain experience met their expectation (P = 0.038) (35).

Many institutions have restricted the utilization of IV acetaminophen because of its cost, resulting in an increase in rectal and enteral acet-

aminophen use in both the preoperative and postoperative periods. There is limited literature comparing the safety and efficacy of IV versus enteral or rectal routes of acetaminophen administration in cardiac surgery patients. In one study, Pettersson et al. evaluated effects of IV versus oral acetaminophen in coronary artery bypass graft (CABG) patients (36). Patients were randomly assigned to receive 1 g of acetaminophen either PO or IV every 6 hours following tracheal extubation once patients could swallow tablets. The authors found that the quantity of opioids administered from the first acetaminophen dose until the next morning in the ICU was significantly less in the IV acetaminophen compared to the oral group. There was no difference in either VAS scores or post-operative nausea and vomiting (PONV) between the two groups (36).

A 2015 systematic review evaluating IV versus oral acetaminophen for the treatment of pain showed that for patients with enteral access, there is no clear advantage for preferentially prescribing IV acetaminophen. The authors noted that 4 of the studies reported pharmacokinetic data that demonstrated that single doses of acetaminophen tablets or elixir achieved high bioavailability. The IV preparation appeared to achieve a greater Cmax and AUC0-6 when compared to enteral preparations in addition to achieving a target plasma concentration of 10 mg/L more often than oral preparations. However, the pharmacokinetic advantages of IV acetaminophen are unclear because the concentration-response relationship of the drug has not been established (37).

Brett et al. tried to establish such a relationship in a study evaluating plasma paracetamol levels following oral or intravenous administration. Despite IV administration achieving higher plasma concentrations, there were no statistically significant differences detected in clinical efficacy (38). Therefore, without strong evidence of clinical efficacy or prevention of opiate-related side-effects, it becomes difficult to justify the additional cost of the IV preparation.

Lidocaine

Perioperative administration of IV lidocaine has been used to treat refractory postoperative pain and to reduce narcotic consumption in surgical patients. Lidocaine is both a local anesthetic and class 1b antiarrhythmic agent and exerts its anesthetic properties by preventing the generation and conduction of nerve impulses thereby increasing the threshold for electrical excitability (Hospira, Inc. Lake Forest, IL, 2010)(39). It has been suggested that systemic lidocaine levels achieved during IV infusion may exert analgesic actions through a different mechanism, such as the disruption of inflammatory signaling or other neuronal actions (40). To date, studies investigating the use of IV lidocaine for the treatment of postoperative pain after a variety of surgical procedures have yielded varying and sometimes conflicting results. There is limited evidence pertaining to its use for the treatment of postoperative pain in cardiac surgical patients.

Initial studies examining the use of lidocaine infusion in cardiac surgery were directed at patients undergoing CABG. Insler et al. examined the perioperative effects of lidocaine on visual analog pain score (VAS), hemodynamics, sedation score, mean total dose of fentanyl, midazolam and propranolol, time to extubation, ICU length of stay, and hospital length of stay. Patients in the study were randomized to receive either placebo or an initial lidocaine 1.5 mg/kg IV dose followed by an infusion of 30 μg/kg/min throughout operation and for up to 48 hours after operation. The study found no difference in VAPS or hemodynamic parameters between the two treatment arms. Retrospectively, both ICU and hospital lengths of stay did not differ between the two groups. The mean total postoperative doses of fentanyl, midazolam, and propranolol did not differ either (41).

In 2010, Cui et al. evaluated the effects of intraoperative administration of lidocaine 33 μg/kg/min IV on postoperative pain by assessing a four-point verbal rating scale (VRS-4) and postoperative morphine consumption in patients undergoing thoracic surgery. Patients were randomized to receive either intraoperative lidocaine or placebo that was discontinued at the time of skin closure. There were significantly more patients experiencing a VRS score < 1 (0, no pain and 1, mild pain) in the lidocaine group compared to those in the control group at 30 min after extubation (P = 0.047), but not at 90 minutes or 120

minutes after operation. Morphine consumption was also significantly less within 30 min, 30-60 min, and at 120 min in the lidocaine group. Beyond 6 hours after discontinuation of the lidocaine infusion, there was no difference in PCA morphine consumption and there was no patient reported side effects of lidocaine toxicity (42).

In 2015, the Cochrane group reviewed 45 trials involving 2,802 patients that investigated the effect of continuous lidocaine IV infusion on postoperative pain assessed by VAS pain scores. Trials were only included if IV lidocaine was initiated intraoperatively and continued for the duration of the operation. The authors concluded that there was low to moderate evidence supporting the impact of IV lidocaine on VAS pain scores compared to placebo. The effect of IV lidocaine was only observed at early (one to four hours) and intermediate time points (within 24 hours) after surgery and did not persist at late time points (up to 48 hours after operation). Pain reduction was most evident in patients undergoing laparoscopic or open abdominal operations. The authors found no evidence of effect in patients undergoing all other types of operations possibly as a consequence of insufficient sample size. Intravenous lidocaine was found to reduce the time to first flatus, first bowel movement, and risk of paralytic ileus. There was no difference in time to the first defecation when compared to placebo. Positive effects of IV lidocaine were realized on secondary outcomes such as hospital length of stay, postoperative nausea, and perioperative opioid requirements (42, 43).

Regional and Neuraxial Techniques

Regional and neuraxial anesthetic and analgesic techniques are currently being used in a wide variety of operations as the sole anesthetic or as an adjunct to manage intra - and post-operative pain. Although epidural and spinal anesthetics have been used effectively for pain management in cardiac surgical patients, the need for systemic heparinization poses a risk of hemorrhagic complications that make it difficult to justify their incremental benefit (44,45).

More recently, there is increased interest in the use of paravertebral blocks (PVBs) that can be performed as a single shot or as a continuous infusion of local anesthetic through a catheter for the treatment of postoperative pain. Although most studies have examined the effectiveness of PVBs in thoracic surgery, only limited data are available with regards to its use in cardiac operations (36). In 2003, Cantó et al reported the results of a prospective study of 47 consecutive patients, who were successfully treated with bilateral paravertebral continuous blocks for on-pump cardiac operations (46). Of the 111 patients studied, 18 patients had complications related to the PVB that included two failed blocks, nine vascular punctures, one pneumothorax, three cases of transient postoperative paresthesias, and three patients with persistent somnolence that improved when the infusion was decreased or discontinued. Despite the frequency of complications, the authors reported excellent analgesia in the patients who had working PVB's with only five patients requiring supplemental IV opioids for breakthrough pain. The clinical application and efficacy of advanced regional anesthetic techniques for the management of postoperative pain in cardiac surgical patients appears promising, but additional experience with these techniques is necessary before they can be recommended for routine use in cardiac surgical patients.

A Multimodal Regimen for the Management of Postoperative Pain in Cardiac Surgical Patients

Recent evidence and accumulating clinical experience is proving that multimodal, narcotic-sparing analgesic medical regiments can provide effective postoperative pain management and contribute to speeding convalescence after major operations. These ERAS protocols stress the importance of opioid-sparing practices that decrease the risk of narcotic-associated adverse effects and take advantage of synergism by incorporating other drug classes, often in reduced doses together with regional or neuraxial anesthetic techniques. However, co-morbidities inherent in cardiac surgical patients combined with the complexity of operations, need for anticoagulation, the potential for postoperative complications, and safety concerns mandate a conservative approach that has delayed the development and implementation of ERAS protocols and limited the

types of drugs and range of techniques that can be routinely employed to treat postoperative pain in this patient population.

Based on the existing evidence, opioid analgesics have a record of safety and efficacy for the treatment of postoperative pain in cardiac surgical patients, but pose side effects that may limit the dose that can be administered to achieve effective analgesia when used alone, delay convalescence, and increase the risk of long-term dependence in susceptible patients. Despite these potential disadvantages, opioid analgesics are still necessary and effective agents for providing postoperative analgesia to most cardiac surgical patients. Opioid analgesics should continue to be used for the treatment of breakthrough pain, but efforts should be made to limit the routine administration of opioid analgesics for maintenance analgesia by prescribing them in combination with non-narcotic analgesics.

The existing evidence supports that NSAID are effective agents used alone or in combination with opioid analgesics for the treatment of postoperative pain, but there are significant safety concerns regarding the routine prescription of NSAID agents for cardiac surgical patients because they may contribute to the risk of postoperative myocardial ischemia, gastritis, acute kidney injury, and bleeding. Although clinical studies appear to support an incremental safety benefit of selective COX-2 inhibitors, bias remains concerning the cardiovascular safety of this class of agents and additional studies are required to clearly delineate the safety of NSAIDs in cardiac surgical patients. The current consensus was to limit the use of NSAIDs to younger patients and those without pre-existing kidney disease who are at low risk for postoperative myocardial infarction or bleeding. There was insufficient evidence to suggest a superiority of selective COX-2 inhibitors until additional clinical experience becomes available. When NSAIDs are prescribed for the treatment of postoperative pain in cardiac surgical patients, efforts should be made to use the lowest effective dose, limit the duration of therapy, and monitor the patient closely for evidence of acute kidney injury, myocardial ischemia, and postoperative bleeding.

Ample evidence supports the safety and efficacy of acetaminophen for the treatment of postoperative pain and this agent appears to be well tolerated with few clinical contraindications in the cardiac surgical patient population. For this reason, it was recommended that acetaminophen be prescribed routinely on a scheduled basis for all cardiac surgical patients who have normal hepatic function. Although evidence supports the efficacy of intravenous acetaminophen for the treatment of postoperative pain, policies to encourage the use of acetaminophen preparations that can be administered enterally or rectally is much more cost-effective.

The consensus of the task force was that gabapentin is an effective off-label option to be routinely included the postoperative pain treatment regimen for cardiothoracic surgical patients, but its dose should be adjusted based on patient age and pre-existing renal function to avoid oversedation. There was insufficient evidence to justify the routine preoperative administration of gabapentin prior to cardiac operations.

The risk-benefit profile of ketamine favors its routine use as an adjunct to general anesthesia that has the potential to decrease postoperative opioid requirements. Ketamine may also be effective for the treatment of breakthrough pain in the postoperative period, but some patients may be disturbed by its dissociative and psychometric effects. Additional studies are necessary to determine if very low doses of ketamine can provide short- and long-term analgesia with a lower incidence of side effects. This approach is consistent with intensive care unit (ICU) best practice guidelines that recommended non-opioid analgesics, such as ketamine, be considered for the treatment of postoperative pain to decrease or eliminate the amount of opioids administered and to decrease opioid-related side effects, Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria +1c and +2C, respectively (47). Policies permitting ketamine to be prescribed by physicians in CVICU and to be administered to patients by the CVICU nursing staff were developed to implement a postoperative analgesic regimen that included ketamine.

Evidence on the safety and effectiveness of intravenous lidocaine for the treatment of postoperative pain was less convincing. There was also a perceived potential risk for lidocaine toxicity

Table 3. Postoperative Pain Regimen Medication Breakdown (33).

Drug	Class	Mechanism of action	Contraindications	Common adverse effects (>5%)
Acetaminophen	Analgesic, nonopioid	Inhibition of CNS prostaglandin synthesis	Severe hepatic impairment; hypersensitivity to drug	Nausea, vomiting, insomnia, pruritic, constipation
Gabapentin	Anticonvulsant; GABA analog	Unknown; structurally related to GABA neurotransmitter	Hypersensitivity to drug	Dizziness, drowsiness, ataxia, fatigue, peripheral edema, tremor, diarrhea, xerostomia, infection, weakness, nystagmus, diplopia
Hydromorphone, IV	Analgesic, opioid	Binds opioid receptors in CNS inhibiting ascending pain pathways	Significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; gastrointestinal obstruction; hypersensitivity to drug	Pruritus, constipation, nausea, vomiting, asthenia, dizziness, headache, dependence
Ibuprofen	Analgesic, nonopioid; NSAID	Reversible inhibition of COX-1 and 2 enzymes	Asthma, urticaria, or other allergic-type reaction following ASA or NSAID; CABG surgery; hypersensitivity to drug	Rash, hypoalbuminemia, gastritis, heartburn, acute kidney injury, myocardial infarction, platelet dysfunction, nausea, dizziness, tinnitus
Ketamine, IV	General anesthetic	Noncompetitive NMDA receptor antagonist	Conditions where significant elevations in blood pressure would be a serious hazard; hypersensitivity to drug	Emergence from anesthesia, hypertension, tachycardia, psychiatric signs or symptoms
Ketorolac, IV	Analgesic, nonopioid; NSAID	Reversible inhibition of COX-1 and 2 enzymes	Bleeding risk; CABG surgery; cerebrovascular bleeding; concomitant NSAID, pentoxifylline, asa, or probenecid; Recent or current GI bleeding / perforation; hemorrhagic diathesis; hemostasis, incomplete; labor and delivery; neuraxial administration; nursing mothers; peptic ulcer disease; renal impairment (or risk of due to volume depletion); prior to major surgery; hypersensitivity or history of asthma, urticaria to other NSAIDs, asa, EDTA, or ketorolac	Headache, gastritis, gastrointestinal pain, dyspepsia, platelet dysfunction, acute kidney injury, myocardial infarction, nausea, dizziness, drowsiness, diarrhea, edema, hypertension, pruritic, rash
Lidocaine, IV	Antiarrhythmic agent, class Ib; local anesthetic	Blocks initiation and conduction of nerve impulses via sodium channel blockaded; class Ib antiarrhythmic	Hypersensitivity to drug or another amide local anesthetic; Adam-Stokes syndrome; Wolff-Parkinson-White syndrome; severe degrees of SA, AV or intraventricular heart block	Local anesthetic toxicity, Erythema, petechiae, pruritus
Oxycodone	Analgesic, opioid	Binds opioid receptors in CNS inhibiting ascending pain pathways	Significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; gastrointestinal obstruction; hypersensitivity to drug	Drowsiness, dizziness, pruritus, nausea, constipation, vomiting, fever, orthostatic hypotension, abnormal dreams, headache, somnolence

CNS, central nervous system; GABA, gamma-aminobutyric acid; IV, intravenous; NSAID, non-steroidal anti-inflammatory drug; COX, cyclooxygenase; asa, aspirin; NMDA, N-methyl-D-aspartate receptor; CABG, coronary artery bypass grafting; GI, gastrointestinal; EDTA, ethylenediaminetetraacetic acid; SA, sinaoatrial; AV, atrioventricular.

that justified the need to monitor lidocaine plasma concentrations in selective patients. For these

reasons, IV lidocaine was not recommended for the routine treatment of postoperative pain, but

remained a treatment option for patients who continued to suffer breakthrough pain despite a regimen of acetaminophen, gabapentin, and narcotics. Lidocaine iv should be considered an option for the treatment of pain in patients who were not candidates for NSAID's or who did not tolerate gabapentin.

The risk-benefit ratio associated with the use of paravertebral blocks for the treatment of postoperative pain in cardiac surgical patients did not justify their routine use except in special cases. Because the safety and efficacy of paravertebral blocks were highly dependent on the skill and experience of the physician performing the block, only specialists in regional anesthetic techniques were permitted to place and manage these blocks in CVICU patients.

The final consensus protocol for the management of postoperative pain for cardiac surgical patients was based on the evidence that was available in the published literature combined with the expert opinions of the members of the multidisciplinary task force. The protocol was also designed to comply with a hospital-wide initiative to standardize and promote safety-, value-, and quality-based patient care. Specific characteristics and profiles of the medications included in the order set are listed in Table 3. The standard order set created from the protocol also limited the range and choices of drugs within specific categories that could be administered to comply with guidelines by The Joint Commission (Tables 1 and 2). To accomplish this, PO acetaminophen was administered preoperatively, ketamine and fentanyl were administered intraoperatively, and a standing regimen of acetaminophen was started immediately after surgery as soon as the patient could tolerate oral medications. Gabapentin was administered in doses that were adjusted to patient age and renal function with further adjustments based on the patient's level of sedation. Providers were limited to selecting only one PO opioid (oxycodone) and one IV opioid (hydromorphone) based on clear parameters provided to the nursing staff to treat breakthrough pain. Hydromorphone could also be ordered to be administered as an IV-PCA regi-

men for appropriate patients. Patients meeting specific clinical criteria were permitted to receive a dose - and duration-limited regimen of NSAID (ibuprofen or ketorolac) with the approval of the attending surgeon. Policies were implemented to permit the prescribing and administration of ketamine or intravenous lidocaine for patients with refractory pain. An educational program for both patients and healthcare providers was emphasized to assess and record patient satisfaction pain scores and level of sedation to calibrate expectations and adjust treatment to provide satisfactory pain control.

Conclusions

Multimodal narcotic-sparing postoperative analgesic regimens used in established ERAS protocols designed for non-cardiac surgical patients had to be modified for use in the cardiac surgical population. Managing postoperative pain in cardiac surgical patients posed unique and specific challenges and there was limited high-quality published evidence to support specific practices. Despite limitations, it was possible to achieve multidisciplinary consensus in the design of a multimodal analgesic regimen to move away from a practice that was predominantly opioid-based. The multimodal analgesic protocol was implemented through a standard order set within the electronic health record and was widely accepted. The preliminary experience showed that the analgesic regimen was effective in decreasing the range and doses of narcotics prescribed for the treatment of postoperative pain and was effective at decreasing the utilization and pharmacy costs associated with the use of intravenous acetaminophen. Further investigation is necessary to understand the impact of the multimodal analgesic regimen on patient satisfaction scores, the incidence of drug-induced adverse events, CVICU length of stay, hospital length of stay, and readmission rates.

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