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Review

Multimodal Analgesia Strategies for Cardiac Surgery: A Literature Review

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Abstract: In cardiac surgery, poststernotomy pain is a significant issue, peaking within 48 h and requiring proper analgesia for both acute relief and avoidance of chronicization. Opioids are commonly used for pain management postsurgery but pose risks such as adverse effects and dependency. Post-cardiac surgery pain can stem from various sources—somatic, visceral, and neuropathic—making opioid reliance a concern. Multimodal analgesia, which combines different medications and regional anesthesia techniques, is increasingly recommended to decrease opioid use and its related problems. Strategies include acetaminophen, gabapentinoids, NMDA antagonists, alpha-2 agonists, intravenous lidocaine, anti-inflammatory drugs, and regional anesthesia. These approaches can enhance pain control, reduce opioid reliance, and improve cardiac surgery outcomes. The ERAS® Cardiac Society strongly advocates for an opioid-sparing multimodal approach to improve patient recovery by reducing complications and increasing patient satisfaction. This review aims to consolidate current evidence to assist healthcare providers in customizing pain management for patients post-cardiac surgery, emphasizing reduced opioid use and optimizing the recovery process.

Keywords: pain; postoperative; cardiac surgical procedures; analgesics; opioid; enhanced recovery after surgery; perioperative care; regional anesthesia; multimodal analgesia; adjuvants

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1. Introduction

Pain after cardiac surgery (CS), ranging from moderate to severe, is reported by up to 60% of patients in the first 2 days [1], with persistent postoperative pain affecting 37% of patients in the first 6 months after CS and 17% of patients beyond 2 years after CS [2]. As a result, poor control of postoperative pain can worsen patients' quality of life, since improvements in cardiovascular symptoms after CS may be minimized by the chronic nature of postoperative pain [3].

Despite advances in cardiovascular surgery, with minimally invasive CS and transcatheter valve therapies, acute pain after traditional open surgery still peaks during the first 48 h. This pain after CS is due to post-cardiac surgery trauma, including sternotomy, sternal retraction, radial artery/saphenous vein dissection and harvesting, and chest tube insertion [4].

Traditionally, postoperative pain management relies on opioid administration. In CS, opioids are the cornerstone of anesthesia, with reports of intraoperative dosages as high as 3 $mg \cdot kg^{-1}$ of morphine [5] or 100 $mcg \cdot kg^{-1}$ of fentanyl [6]. Although opioids are effective, relatively inexpensive, and available in various pharmaceutical forms, the adverse effects typically associated with opioids, such as sedation, respiratory depression, or paralytic ileus, can delay and impair postoperative recovery [4].

Furthermore, opioid abuse has been identified as a significant cause of morbidity and mortality in the United States, with postoperative opioid use being a contributing factor [7]. A recent study revealed that, after CS, almost 10% of patients continued to use opioids for more than 90 days after surgery, and the higher the prescribed opioid dose at discharge was, the greater the risk of persistent postoperative opioid use [8].

Therefore, measures such as multimodal analgesia strategies have been implemented to reduce opioid use, especially in opioid-naive patients [7]. However, reducing the use of opioids poses a challenge for healthcare providers, as inadequately controlled postoperative pain can be as high as 80% and can lead to chronic pain syndrome, continuous opioid use, increased morbidity, impaired functionality and quality of life, delayed recovery time, and increased costs to healthcare systems [9].

Multimodal analgesia combines different analgesics and techniques that block or modulate pain stimuli at every point in the pathway from the periphery to the cerebral cortex; this relies on the "aggregation of marginal gains" theory, in which small gains at each stage can result in greater improvements that may produce superior analgesia while decreasing opioid use and opioid-related side effects [7,10]. The administration of acetaminophen, gabapentinoids, NMDA antagonists, alpha-2 agonists, lidocaine, nonsteroidal and steroidal anti-inflammatory drugs, or regional nerve block techniques are the most commonly used approaches [11]. On the basis of these documented benefits, the Society for Enhanced Recovery After Cardiac Surgery (ERAS® Cardiac) strongly recommends the inclusion of an opioid-sparing multimodal strategy [12] and has recently published updated recommendations specifically addressing postoperative analgesia in patients with CS [13]. The implementation of cumulative anesthesia-related strategies, which mainly focus on multimodal analgesia, indeed improved rates of early extubation and affected the duration of stay after CS in the ERACS scenario [14].

Considering the significance of postoperative pain control in cardiovascular surgery, particularly through reducing opioid use and potentially incorporating regional anesthesia techniques, this article aims to present the main multimodal analgesia strategies for postoperative CS through a literature review.

2. Materials and Methods

This is a literature review in which primary articles published preferably within the last 10 years were considered eligible for evidence-based medicine assessment, except for the articles used as references for background and theoretical concepts that were selected regardless of publication date. Only articles published in Portuguese, English, or Spanish were selected, and the following reference databases were used: Biblioteca Virtual de Saúde (BVS), Web of Science; CAPES; SciELO; PubMed; and LILACS. The search strategy used the following keywords or MeSH (Medical Subject Headings): "Pain, Postoperative"; "Cardiac Surgical Procedures"; "Analgesics, Opioid"; "Enhanced Recovery After Surgery"; "Perioperative Care"; "Regional Anesthesia"; "Multimodal analgesia"; "Adjuvants, Pharmaceutic"; "Adrenergic alpha-2 Receptor Agonists"; "Methadone"; "Ketamine"; "Lidocaine"; "Anti-Inflammatory Agents, Nonsteroidal"; "Acetaminophen"; "Gabapentin"; and "Pregabalin". After each database was searched, duplicate references were excluded. In this manner, 923 articles were selected for review, and 85 were included in the writing of this review.

Within the context of evidence-based medicine, critical appraisal of articles is an essential skill for evidence-based practice, with a focus on mitigating biases and integrating the best external evidence into clinical care. Several meta-analyses and clinical trials have served as models for the development of various health guidelines, particularly in the context of postoperative pain control management in conventional cardiovascular surgery, generating various speculations in the scientific community regarding therapeutic measures involving the use of opioids, multimodal analgesia, and adjunct therapy [15].

Critical appraisal tools (CATs) were utilized in the selection of the 85 articles in this review. CATs are structured checklists that assess the methodological quality of a study on the basis of a set of 20 criteria. CATs are based on algorithms to understand the study design

type, three separate tools (for analytical studies, descriptive studies, and literature reviews), additional tools to support the evaluation process, and guidance for synthesizing evidence and drawing conclusions on a specific topic's evidence scope. Although the toolset was developed to assist in creating national guidelines associated with infection prevention and control, physicians, reviewers, and academics can use it to assess any quantitative health-related research [15]. To be included in the review, the study should fulfill at least 80% of the set of 20 criteria and have at least 80% consensus between the authors.

Following the evaluation of individual items in each study type, each CAT also provides requirements for inferring an overall conclusion about the study's evidence quality on the basis of item evaluation. Quality is categorized as high, medium, or low. While a randomized clinical trial is a strong study design, it is possible to have a low-quality trial or a high-quality study. Therefore, a study's evidence quality distinguishes itself from study design strength when evaluating the overall evidence quality.

3. Results

3.1. The Basic Pathophysiology of Pain

Pain after CS can arise from various sources, such as visceral, musculoskeletal, or neurogenic origins (Table 1). Visceral pain from the heart reaches the central nervous system through pathways involving the vagus nerve, cervical sympathetic chain, and upper-thoracic sympathetic ganglia. Most pain related to heart issues postsurgery is due to inadequate blood supply (ischemia) caused by conditions such as coronary artery vasospasm, atherosclerosis, or acute insufficiency [16].

Table 1. Types and topography of pain after cardiac surgery.

Superficial
• Skin incisions
• Drainage and dissection/puncture sites
Musculoskeletal
• Sternal and costal fractures
• Sternoclavicular and acromioclavicular joints
• Zygapophyseal, costovertebral, and cervicothoracic joints
Visceral
• Pericardium
• Pleura
• Myocardium (ischemia)
• Diaphragm
Neurological
• Peripheral nerve injury (for example, radial, saphenous)
• Nervous confinement
• Nervous plexus injury (for example, brachial)

The most common persistent pain following CS typically arises from myofascial structures such as muscles, bones, tendons, and ligaments. In addition to the impact of surgical trauma, which activates peripheral neurons and releases chemical mediators such as histamine and serotonin, pain can also be influenced by patient positioning during surgery and the use of surgical instruments. For example, a sternal retractor can lead to complications such as fractured ribs, dislocation of the costochondral junction, costochondritis, and rib–spine articulation issues [16].

Furthermore, harvesting the internal mammary artery during procedures such as coronary artery bypass has been linked to a specific neuropathic pain syndrome postsurgery. This pain is believed to arise from nerve injuries resulting from the procedure, leading to an irritated state referred to as neuritis. Symptoms of this pain may include burning or lancinating sensations, worsening at night, and exacerbation upon stretching the affected nerve. Patients may also experience muscle twitching, hypersensitivity, abnormal

sensations (paresthesia), or altered sensation to touch (dysesthesia) [16]. Commonly used incisions include cervical, thoracic, and lumbar dermatomes (Figure 1).

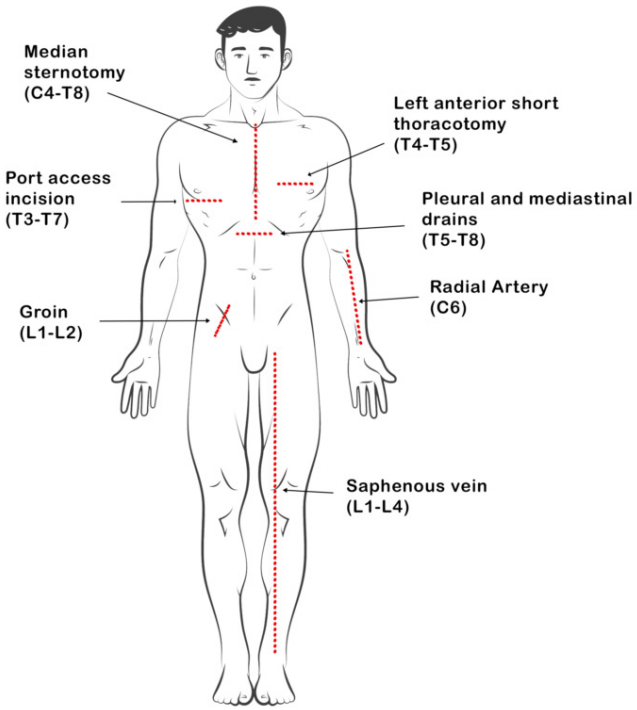

Figure 1. Sites of incisions in cardiovascular surgery associated with postoperative pain. C—cervical level; T—thoracic level; L—lumbar level. Adapted from [17].

3.2. Opioids

Opioids, as already discussed, are effective for acute pain treatment and, in this respect, are widely used after surgery, including CS. The side effects of the use of this class of drugs are repeatedly observed in both acute and chronic use. These include constipation, postoperative nausea and vomiting (PONV), respiratory depression, and hyperalgesia. In addition, tolerance develops with chronic use of opioids, in which higher doses are required to acquire the same analgesic effects. Moreover, opioids can even decrease the rate of wound healing [18].

Recent recommendations in the ERACS are based on an "opioid stewardship" approach, which involves the careful and appropriate utilization of opioids to manage surgical pain effectively and enhance postoperative recovery outcomes [13]. Despite concerns regarding opioid-related adverse events and persistent opioid use, opioids continue to play a vital role in managing acute pain and providing intraoperative anesthesia. Opioid stewardship emphasizes the importance of using opioids judiciously to ensure patient comfort, promote functional recovery, and avoid compromising optimal pain control.

Although there is a trend toward reducing opioid use in cardiac surgeries and ERAS settings, methadone, despite being classified as an opioid, has emerged as an attractive alternative with a unique profile within the multimodal strategy. First, owing to its prolonged action (24–36 h of efficacy with a single dose), it can promote more stable basal control of acute pain during this period of intense painful stimuli [19]. Its activity on the NMDA receptor is also considered a potential mechanism for improved quality and more consistent control of pain in the postoperative period following cardiac and noncardiac procedures in adults, and some evidence supports the hypothesis that NMDA receptor antagonism may reduce the development of chronic pain syndromes [19,20]. Additionally, methadone inhibits the reuptake of the neurotransmitters serotonin and norepinephrine in the CNS and may provide a mood-elevating effect postoperatively as well as act on inhibitory descending pain pathways [21].

A systematic review revealed that, compared with the administration of morphine or fentanyl, the intraoperative administration of methadone decreased postoperative acute pain and reduced opioid consumption [22]. These findings confirmed that methadone could be used as an opioid during cardiothoracic procedures to alleviate acute postsurgical pain. In line with this study, other authors have assessed the effects of intraoperative intravenous methadone in patients who underwent CS on postoperative opioid requirements and surgical recovery. Methadone is safe and significantly reduces intraoperative and postoperative opioid needs in the first 24 h after surgery [23].

The largest clinical trial assessing methadone in CS compared patients randomized to receive either 0.3 $mg \cdot kg^{-1}$ methadone or 12 $\mu g \cdot kg^{-1}$ fentanyl intraoperatively, and those in the methadone group had reduced postoperative morphine requirements, improved pain scores, and increased patient-perceived quality of pain management without increasing adverse events [24]. In a follow-up study, a pain questionnaire assessing weekly frequency (primary outcome) and pain intensity at 1, 3, 6, and 12 months postsurgery was administered. The results revealed that patients randomized to receive methadone for CS reported a lower postoperative pain frequency even at 1 month than patients randomized to receive fentanyl [25].

In pediatric patients, an observational prospective study revealed that intraoperative methadone use at doses up to 0.4 $mg \cdot kg^{-1}$ was associated with a decrease in perioperative opioid exposure in patients undergoing congenital heart surgery and was not associated with adverse events, prolonged mechanical ventilation, or intensive care unit stay [26].

Considering methadone as a component of multimodal analgesia, a recent retrospective study in adult cardiac surgery patients compared three analgesic regimens: an opioid-only regimen with intraoperative fentanyl and patient-controlled analgesia and two multimodal regimens. Multimodal regimen 1 included preoperative oxycodone, intraoperative ketamine, and postoperative morphine suppository, while multimodal regimen 2 involved intraoperative methadone infusion and dexmedetomidine. The multimodal analgesic regimens, particularly those incorporating methadone and dexmedetomidine, significantly reduced total opioid usage and predischarge opioid consumption in cardiac surgical patients [27].

Owing to the abovementioned evidence, methadone has been considered one of the most effective strategies for controlling postoperative pain after CS (Figure 2) [13]. Methadone may be an opioid that greatly limits the use of other opioids and has a promising role in enhanced recovery protocols [28]. These recent findings have led to increased utilization of methadone over time. This trend aligns with the implementation of enhanced recovery pathways, affirming improved pain management post-cardiac surgery with minimal side effects [29].

Tramadol is another opioid medication that is worth mentioning in multimodal analgesia for CS, as it was first recommended in the ERACS guidelines [12]. Tramadol is a centrally acting analgesic with a dual mechanism: it acts on the mu-receptor and inhibits serotonin and noradrenaline reuptake at the central synaptic level. Unlike traditional opioids, tramadol does not affect hemodynamic or respiratory function, nor does it cause tolerance [30]. Its recommendation for postoperative analgesia in patients with CS results from an old clinical trial that reported a 25% reduction in postoperative morphine consumption after a single dose prior to extubation [31]. A more recent study showed that, in combination with oral acetaminophen, tramadol improved analgesia and reduced the morphine requirement up to 50% after coronary artery bypass surgery [30].

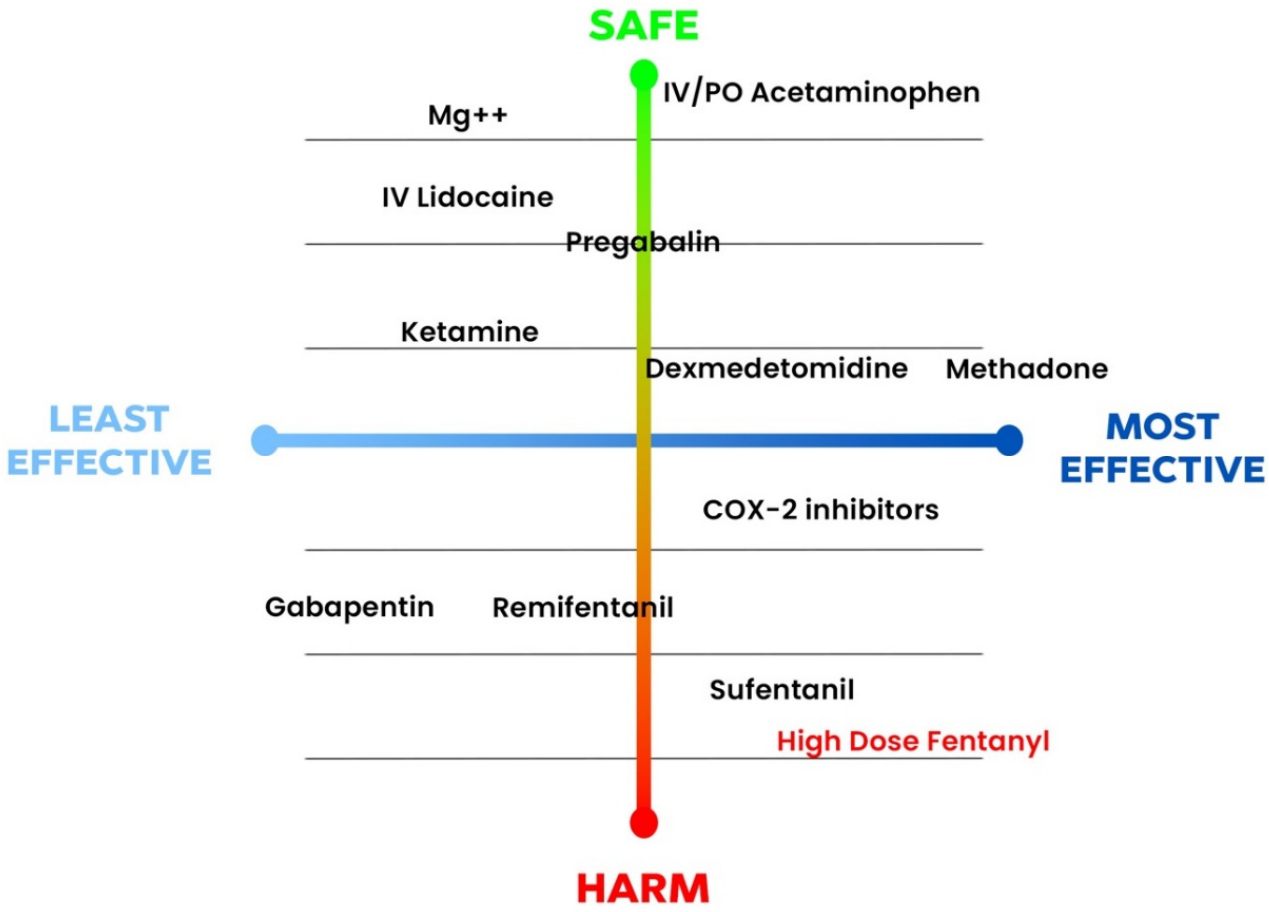

Figure 2. Efficacy and safety of multimodal analgesics after CS. COX-2: cyclooxygenase type 2; IV: intravenous; PO: per os/oral; Mg++: magnesium sulfate. Adapted from [13].

3.3. Paracetamol/Acetaminophen

Paracetamol is generally used as an adjuvant analgesic with central properties and has been shown to reduce inflammation in the perioperative setting; however, it is not commonly studied in CS, except for intravenous formulations. The DEXACET trial revealed that paracetamol reduced opioid consumption, produced similar pain scores, and potentially reduced delirium, possibly as a consequence of poor pain control or opioid side effects [32]. Another trial in CS compared 1 g of intravenous acetaminophen every 6 h for 24 h with a placebo and reported reduced pain but not opioid consumption in the acetaminophen group after CS [33].

In the oral formulation, acetaminophen (375 mg) in combination with tramadol (37.5 mg) reduced cumulative morphine consumption after CS by 50% [30] when given preoperatively and every 6 h until 48 h postoperatively [30]. The relative cost-effectiveness of oral administration compared with intravenous administration is controversial; therefore, despite the higher bioavailability of the intravenous form, oral paracetamol is encouraged in major surgery (maximum dose, 3–4 g/24 h) unless contraindicated owing to an inability to tolerate oral medication or in the presence of significant liver dysfunction [34]. Owing to this evidence and safety profile, acetaminophen is recommended in the ERACS guidelines at a 1 g dose every 8 h as an opioid-sparing strategy [12].

3.4. Gabapentinoids

Gabapentin is an amino acid and an analog of gamma-aminobutyric acid (GABA) that was found to be effective as an anticonvulsant drug. Pregabalin is another GABA analog closely related to gabapentin. Both medications are also used as adjunctive therapies in pain management. Despite their close structural resemblance to GABA, gabapentin and

pregabalin do not directly act on GABA receptors. Both drugs bind to the α2δ subunit of voltage-gated N-type calcium (Ca^{2+}) channels. This phenomenon appears to form the basis of their primary mechanism of action, which involves reducing Ca^{2+} influx, predominantly affecting presynaptic channels in the dorsal horn of the spinal cord [35].

In one of the most emblematic trials assessing gabapentin, a preoperative single dose (600 mg) reduced opioid consumption and improved pain scores compared with placebo, but at the expense of increased sedation and an increase in postoperative mechanical ventilation [36]. Conversely, another study found that a higher preoperative dose of gabapentin (1200 mg) followed by scheduled doses (600 mg twice daily for two postoperative days) resulted in similar opioid consumption and pain scores, with no difference in side effects [37].

Pregabalin is considered a successor to gabapentin. Compared with placebo, the administration of 150 mg pregabalin preoperatively followed by 75 mg pregabalin twice a day for 5 days reduced postoperative opioid consumption but increased the time to extubation after CS. Three months after the operation, patients in the pregabalin group experienced less pain during movement [38]. Another study revealed that the same pregabalin schedule, however, until 48 h postoperative, reduced both pain scores and the consumption of tramadol in the postoperative period without delaying extubation and causing excessive sedation [39].

In a study of adults without chronic pain who underwent any elective CS with sternotomy, groups were randomized to receive either pregabalin alone (150 mg preoperatively and twice daily for 14 days) or pregabalin combined with a 48 h postoperative ketamine infusion (0.1 $mg \cdot kg^{-1} \cdot h^{-1}$). The study found that the prevalence of pain was significantly lower in both the pregabalin-alone and pregabalin-plus-ketamine groups compared to the control group at both 3 and 6 months postsurgery [40].

A meta-analysis in cardiac surgery found that pregabalin reduced postoperative pain scores and opioid consumption without increasing mechanical ventilation duration, sedation, or other side effects. In contrast, gabapentin did not reduce opioid consumption but may have lowered pain scores, potentially at the cost of prolonged mechanical ventilation [41]. In summary, with respect to gabapentinoids, pregabalin is preferable and is recommended as an opioid stewardship strategy [13].

3.5. N-methyl-D-aspartate (NMDA) Receptor Antagonists

Ketamine is a derivative of phencyclidine that is partially water soluble and highly lipophilic. Among the two stereoisomers of ketamine, the S(+) isomer is more potent than the R(−) isomer. The main observed effect is likely produced by the inhibition of the N-methyl-D-aspartate (NMDA) receptor complex. The use of ketamine has always been limited because of its unpleasant psychotomimetic side effects. However, this drug represents a relevant alternative in certain circumstances, mainly because of its potent analgesic effects with minimal respiratory depression [42].

The role of ketamine as an adjuvant for pain management in CS dates back to the early 2000s, when a small-dose S(+)-ketamine infusion, as an adjunct to PCA oxycodone, exerted an opioid-sparing effect without hemodynamic side effects after sternotomy and improved patient satisfaction in CABG patients [43]. However, recent trials have shown that either a single induction bolus of 0.5–1.0 $mg \cdot kg^{-1}$ [44] or a bolus of 0.5 $mg \cdot kg^{-1}$ followed by a continuous infusion of 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ [45] were not able to reduce pain scores, opioid consumption, or delirium after CS. In one of these studies, patients who received ketamine had more negative experiences [44].

In the context of CS, the results diverge from those in noncardiac settings, wherein perioperative intravenous ketamine reduces postoperative analgesic requirements and pain severity across various surgical procedures and administration timings, irrespective of study size or pain intensity levels. Central nervous system (CNS) adverse events exhibited minimal disparity between the ketamine and control groups. Perioperative intravenous ketamine likely marginally reduces PONV [46]. In addition, a previously mentioned study revealed that ketamine infusion combined with pregabalin resulted in less chronic pain

after 3 and 6 months than pregabalin alone [40]. Although it is included as an opioid-sparing strategy in pain management after CS [13] and has been shown to be one of the process measures that effectively reduces the intubation time and length of stay (through an intraoperative infusion of 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$) [14], more studies are needed to further prove its effectiveness.

3.6. Alpha-2 Agonists

Dexmedetomidine is a highly selective α2-adrenergic agonist. This drug is the active S-enantiomer of medetomidine, a highly selective α2-adrenergic agonist imidazoline derivative. Dexmedetomidine produces its selective α2-agonist effects by activating α2 receptors in the CNS causing hypnosis by stimulating α2 receptors in the locus coeruleus and providing analgesia through activation of α2 receptors in the spinal cord. Its sedative effects are associated with the activation of endogenous sleep pathways [47].

Intravenous dexmedetomidine has demonstrated benefits such as earlier extubation, reduced arrhythmias and delirium, and shorter hospital stays in CS [48,49]. It also shows promise as an analgesic, reducing opioid requirements and improving pain management for up to 24 h postsurgery [50,51]. It has been recommended as a component of the stewardship opioid strategy after CS in the ERACS context at 0.5–1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ [12,13]. Dexmedetomidine at 0.2–0.7 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion, administered at the time of cardiopulmonary bypass and throughout transport to the ICU, was one of the process measures that effectively reduced the time to extubation and length of hospital stay in one hospital during ERACS implementation [14].

A recent large trial with almost 800 patients assessing the effectiveness of dexmedetomidine in reducing atrial fibrillation and postoperative delirium reported disappointing results. Dexmedetomidine infusion, initiated at anesthetic induction and continued for 24 h, did not decrease postoperative atrial arrhythmias but increased delirium in patients recovering from CS. In addition, patients who received dexmedetomidine had more clinically important hypotension episodes, which might be the cause of increased delirium [52]. Although well designed, this study has points of concern, as both anesthesia techniques and medications were not standardized, as intraoperative opioids and benzodiazepines were given at the discretion of the anesthesiologist. Moreover, anesthesia is usually induced with midazolam, thiopental, etomidate, propofol, and sufentanil or fentanyl, or both. The absence of standard anesthetic techniques can make delirium assessment and quantification of postoperative opioid consumption difficult.

3.7. Dexamethasone and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are a unique group of medications that target cyclooxygenase (COX), an enzyme essential for prostaglandin (PG) biosynthesis from arachidonic acid. COX has two isoforms: COX-1, which is found in most tissues and plays a role in various bodily functions, and COX-2, which is present in inflammatory cells and produces proinflammatory mediators. NSAIDs can either inhibit both COX-1 and COX-2 or selectively inhibit COX-2. Arachidonic acid, which is released in response to stimuli, is converted by COX to produce various PGs, facilitating the inflammatory response mechanism [53].

Prostaglandins are molecules that are released from cells and act locally through G-protein-coupled receptors. The most common type in the body is PGE2, which is continuously produced by COX-1. Inflammation can increase PGE2 production via COX-2. These enzymes have preferences for various prostaglandins. PGE2 and PGI2 play a role in increasing the sensitivity of pain receptors and neurons, contributing to pain perception both in the periphery, by reducing the excitability threshold, and in spinal dorsal horn neurons, by contributing to central sensitization [54].

When included in a multimodal regimen, NSAIDs or COX-2 inhibitors reduce pain and opioid use, potentially decreasing opioid-related side effects [55,56]. In CS, there is enough evidence to support that NSAIDs reduce pain scores and postoperative opioid consumption [57]. However, even with evidence showing adverse events similar to those

associated with placebo [57], concerns about potential renal injuries and gastrointestinal complications limit their widespread use in CS [58]. Similarly, COX-2 inhibitors significantly reduce postoperative morphine consumption and improve pain perception after coronary artery bypass graft; however, this occurs at the expense of an increase in composite adverse events, which are mainly thrombotic in nature [59]. Another study reported that COX-2 inhibitors were associated with an increased incidence of cardiovascular events after CABG [60]. These results are sufficient for the Food and Drug Administration (FDA) to issue a formal alert regarding the use of NSAIDs in patients undergoing coronary revascularization.

Nonetheless, perioperative care physicians are still using NSAIDs selectively in the CS setting, despite the 2005 black box by the FDA. An observational study revealed that one-third of cardiac patients, with a lower preoperative risk, received ketorolac postoperatively for pain control, and no increase in any adverse events was found. The authors concluded that ketorolac appears to be safe for use as a postoperative analgesic when administered selectively after cardiac operations and raised the question of the need for a black box warning against the use of ketorolac for all CS patients [61].

A recent trial in pediatric patients undergoing CS revealed that 10 $mg \cdot kg^{-1}$ ibuprofen, a component of multimodal analgesia, improved postoperative analgesia in terms of reducing opioid consumption and pain scores without increasing renal dysfunction [62]. In adults, a combination of ketorolac intraoperatively and ibuprofen postoperatively for 4 days as components of multimodal analgesic therapy offered significantly better analgesia with significantly less PONV than a traditional opiate regimen [63].

Dexamethasone, a glucocorticoid, offers analgesic benefits likely due to its anti-inflammatory effects and should be included in a multimodal perioperative pain regimen. Meta-analyses show that patients receiving dexamethasone have lower pain scores, reduced opioid use, and need less rescue analgesia [64,65]. In CS, there is concern regarding glucocorticoids due to reference studies evaluating high doses, as high as 1 $mg \cdot kg^{-1}$, of dexamethasone, which have been associated with increased myocardial injury [66] and elevated blood glucose levels [67]. No benefits in reducing mortality were registered, and analgesia was not assessed. There is some evidence that, as a component of multimodal analgesia, a single 8 mg dexamethasone dose can significantly reduce pain and PONV [63], in addition to improving the quality of recovery after CS [68].

3.8. Intravenous Lidocaine

Intravenous (IV) lidocaine infusions may be effective in reducing systemic inflammation and are indicated as part of a multimodal analgesic approach for visceral surgery when regional analgesia is not possible [28]. In this context, a recent meta-analysis revealed that in noncardiac surgery, IV lidocaine was associated with a decrease in postoperative pain and opioid consumption [69,70] and a faster return of bowel function and decreased length of hospital stay [70].

However, in CS studies, intraoperative IV lidocaine has not been shown to affect postoperative pain or opioid consumption [71,72]. One possible mechanism for this difference is that the key mechanism responsible for the analgesic effects of IV lidocaine infusions, its metabolism to a glycine receptor inhibitor causing an antinociceptive effect, may be disrupted by the abrupt changes in glycine concentrations that occur in response to cardiopulmonary bypass [72].

Nonetheless, IV lidocaine reduced the incidence of postoperative cognitive dysfunction after CS when it was administered as a bolus of 1.5 $mg \cdot kg^{-1}$ followed by a 4-$mg \cdot min^{-1}$ infusion in the CS, which increased interest in intraoperative infusion of this medication [73]. However, a larger randomized controlled trial recently reported that IV lidocaine did not affect quality-of-life outcomes 6 weeks after CS. Furthermore, even at the 1-year follow-up, there were no differences in cognitive score changes, cognitive deficits, or quality of life among patients who received IV lidocaine [74]. In summary, the available evidence does not support the use of perioperative lidocaine infusion for CS patients.

3.9. Regional Anesthesia

Regional anesthesia, encompassing both neuraxial and peripheral nerve blocks, plays a crucial role in multimodal analgesia, as it can effectively block pain sensation originating from the site of the surgical incision or manipulation. This process blocks the transmission of action potentials from the periphery to the central nervous system at various points [13]. When performing regional nerve blocks in surgical settings, it is essential to consider the distribution of nerves in both the incision and the drainage sites. Specifically, for procedures such as median sternotomy or thoracotomy, the focus should be on targeting the perforating branches of the intercostal nerves originating from the thoracic spine nerves (T1–T11) [75].

In the past, thoracic epidural analgesia (TEA), spinal anesthesia (SA), and paravertebral blocks (PVBs) were common regional techniques for postoperative pain control. However, issues such as the risk of epidural hematomas from systemic heparinization, hemodynamic instability from sympathetic blockade, technical challenges, and difficulties in managing postoperative pain have reduced their use in cardiac surgical patients [76]. Owing both to these concerns and to the widespread use of ultrasound in regional anesthesia, several regional analgesic techniques have been developed in recent years using different approaches in the thoracic region (anterior, lateral, and posterior), most of which rely on ultrasound-guided fascial plane blocks for the perioperative pain management of patients undergoing CS [76].

The most popular novel ultrasound-guided blocks for CS are erector spinae block (ESPB), serratus anterior muscle plane block (SAPB), pectoral muscle blocks (PECS I and PECS II), transversus thoracis muscle plane block (TTMB), and pecto-intercostal fascial plane block (PIFB) [77]. In view of the various nomenclatures given to the same regional block in the literature, there was recently a Delphi consensus of regional anesthesia experts that resulted in the standardization of block names [78]. Thus, PIFB and TTMB are now referred to as superficial and deep parasternal intercostal plane (PIP) blocks, respectively. In addition, pectoral muscle plane blocks are still a matter of debate, since PECS I had its name changed to an interpectoral plane block and PECS II had its name changed to a pectoserratus plane block; however, there was a low agreement rate between the authors [78].

ESP block and PVB are posterior approaches for fascial plane blocks and normally cover the posterolateral region of the chest, with variable anterior coverage past the midclavicular line [75]. PECS I, PECS II, and SAPB (superficial or deep) are anterolateral approaches that normally cover the lateral region of the chest and are suitable for drains and thoracotomies associated with minimally invasive CS [75,77]. Finally, parasternal intercostal plane blocks, either superficial or deep, are anterior approaches that cover anterior cutaneous intercostal branches well and are suitable for sternotomy (Figure 3) [75,77]. Although the deep parasternal intercostal plane block covers more parasternal interspaces than does the superficial block with a single injection, the proximity to the internal mammary artery and the severe consequences of an arterial injury raise concerns about the deep technique [79].

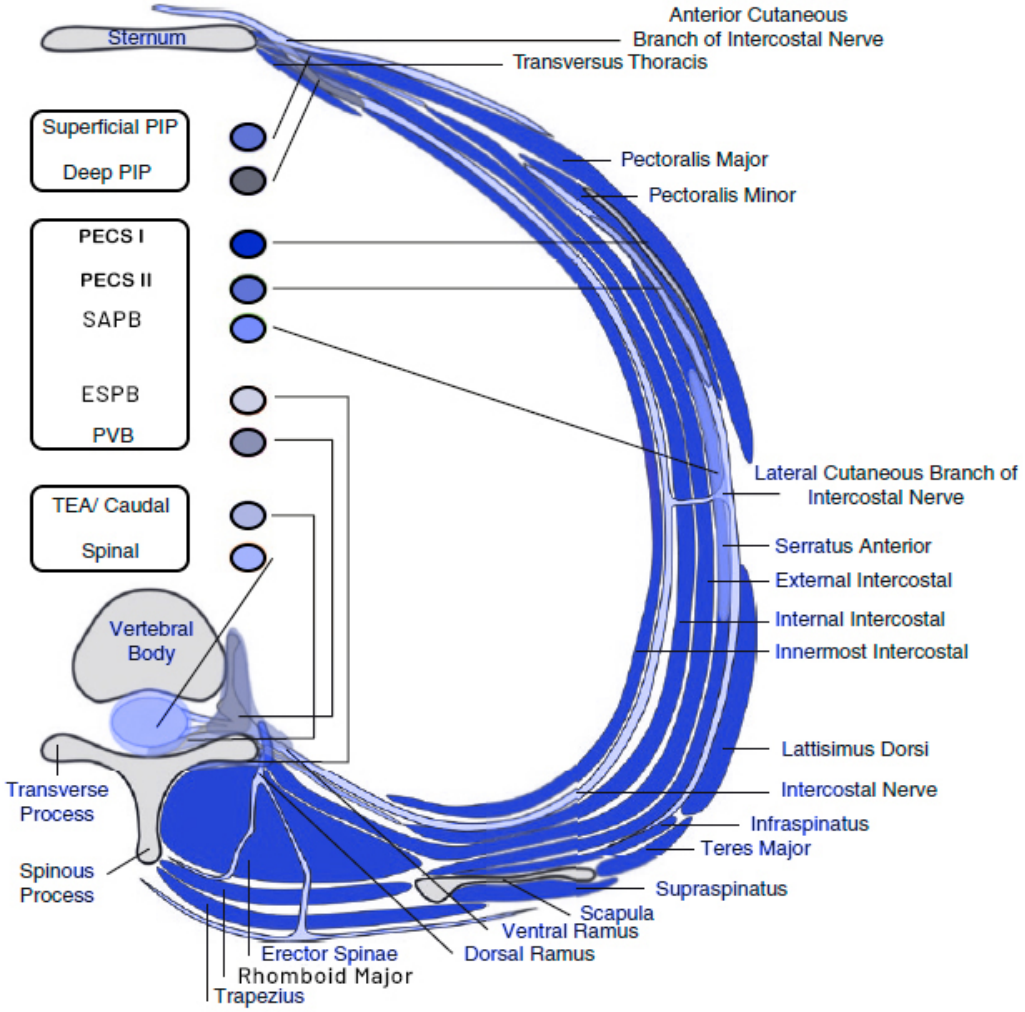

Figure 3. Sites of action for regional anesthesia techniques for CS. Unilateral axial cross section at the level of T5. TEA: thoracic epidural; PIP: parasternal intercostal plane nerve block; PVB: paravertebral block; ESP: erector spinae plane block; PECS I: pectoralis nerve block I, also known as interpectoral plane block (IPP); PECS II: pectoralis nerve block II, also known as pectoserratus plane block (PSP); SAP: serratus anterior plane block. Adapted from [80].

Compared with either placebo or the absence of regional anesthesia, fascial plane blocks of the chest reduce both pain and opioid consumption after CS [81,82]. Among all facial plane blocks, one network meta-analysis showed that, to date, ESPB was the most effective treatment, with a greater reduction in postoperative opioid consumption than the other methods [81]. As a component of multimodal anesthesia, regional blocks are associated with reduced time to extubation and length of stay [14] and should be performed for postoperative pain control in the ERACS context [13]. A summary of all fascial plane blocks is depicted in Table 2.

Table 2. Summary of ultrasound-guided regional nerve blocks in cardiac surgery.

Regional Block	Target	Sensory Distribution	Surgical Approach Pathway	LA Volume for Unilateral Block	Considerations
Paravertebral (PVB)	Paravertebral space (deep to superior costotransverse ligament)	Ipsilateral hemithorax Sympathetic block: yes	Sternotomy (BLB)	20–25 mL if single level (4th TP) or 4–5 mL with multilevel approach	Formal contraindication with anticoagulation. Single level equivalent to multiple-level approach

Table 2. *Cont.*

Regional Block	Target	Sensory Distribution	Surgical Approach Pathway	LA Volume for Unilateral Block	Considerations
Erector spinae plane block (ESPB)	Between ESM and TP	Ipsilateral hemithorax Sympathetic block: yes	Sternotomy (BLB)	20 mL on the 5th TP	Two-level injection to improve the spread of LA.
PECS I or Interpectoral plane block (IPP)	Between pectoralis major and pectoralis minor	Narrow upper antero-lateral chest wall	Minimally invasive thoracotomy (ULB)	10–15 mL on the 3rd rib	Unsuitable for sternotomy
PECS II or pecto-serratus plane block (PSP)	Between pectoralis minor and anterior serratus	Wide upper anterolateral chest wall, including axilla	Minimally invasive thoracotomy (ULB)	20–30 mL on the 3rd to 4th rib	Unsuitable for sternotomy. Perform PECS I after II with a single-pass approach.
Serratus anterior plane block (SAPB)	Supra (between SAM and latissimus dorsi) or Sub-SAM (between SAM and intercostal muscle)	Lateral chest wall	Minimally invasive thoracotomy (ULB)	30–40 mL on 4th to 5th rib	Unsuitable for sternotomy. Anterior spread with deep SAPB; posterior spread with superficial SAPB
Pecto-intercostal fascial plane block (PIFB) or Superficial Parasternal Intercostal Plane block	Between pectoralis major and external intercostal muscle	Parasternal	Sternotomy (BLB)	20 mL on the 4th rib	Multilevel approach
Tranversus thoracis muscle plane block (TTMB) or Deep Parasternal Intercostal Plane block	Between innermost intercostal muscle and Thoracic transversus muscle	Parasternal	Sternotomy (BLB)	20 mL on the 4th rib	Higher spread with a single shot compared to superficial approach. Caution with internal thoracic artery.

PVB, paravertebral block; ESPB, erector spinae plane block; PECS I and II, pectoralis nerve blocks I and II; SAPB, serratus anterior plane block; PIFB, pecto-intercostal fascial plane block; TTMB, transversus thoracis muscle plane block; ESM, erector spinae muscle; TP, thoracic transverse process; SAM, serratus anterior muscle; ULB, unilateral block; BLB, bilateral block; LA, local anesthetic. Adapted from [83].

It is important to mention that mediastinal drain placement sites are outside the area of effect of most chest wall blocks, and that sometimes the sternotomy incision extends below the T6 dermatome. To effectively cover the subxiphoid area, abdominal wall blocks have been studied, and the bilateral rectus sheath block (RSB) is the most suitable [84]. In combination with parasternal intercostal blocks, RSB, which consists of injecting local anesthetic into a fascial plane between the rectus abdominis muscle and its posterior sheath, improved analgesia and reduced postoperative opioid consumption compared with parasternal blocks alone [85,86]. Therefore, the addition of bilateral RSD to chest wall blocks may be a solution to manage subxiphoid pain after cardiac surgery requiring chest drains emerging in the epigastric area. Caution must be taken in the total dose of local anesthetic in these cases, and the addition of adjuvants such as dexamethasone 10 mg may prolong analgesia after a single-shot injection [85].

4. Conclusions

Compared with traditional care, multimodal treatment of pain after CS is feasible and rational and has been associated with improved outcomes. As both the surgical techniques and the technology of devices improve in the CS scenario, the perioperative analgesia strategy must follow these advancements, providing effective pain control without the frequent adverse side effects caused by traditional opioid-based analgesia, as well as providing faster patient recovery. To date, methadone seems to be the most effective opioid-sparing drug for controlling pain after CS; however, it still has opioid-related side effects and should be combined with other strategies, such as gabapentinoids, acetaminophen, low doses of dexamethasone, NSAIDs (in selected cases), dexmedetomidine, and, with

less evidence, ketamine infusion. Although safety concerns have reduced the use of traditional regional anesthesia techniques (spinal anesthesia, epidural, and paravertebral blocks), ultrasound-guided fascial plane blocks have been shown to be effective and safe and, regardless of the chosen technique, should now be a component of the multimodal analgesia strategy following CS recommended by the ERACS. This review has summarized the most up-to-date evidence regarding postoperative analgesia strategies in the CS scenario and reinforces the importance of better-designed clinical studies assessing the impact of multimodal analgesia in ERACS.

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