

## ORIGINAL ARTICLE

# Pain management after cardiac surgery via median sternotomy

## *A systematic review and procedure-specific postoperative pain management (PROSPECT) recommendation*

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**BACKGROUND** Pain after cardiac surgery via median sternotomy can be difficult to treat, and if inadequately managed can lead to respiratory complications, prolonged hospital stays and chronic pain.

**OBJECTIVES** To evaluate available literature and develop recommendations for optimal pain management after cardiac surgery via median sternotomy.

**DESIGN** A systematic review using PROcedure-SPECific Pain Management (PROSPECT) methodology.

**ELIGIBILITY CRITERIA** Randomised controlled trials and systematic reviews published in the English language until November 2020 assessing postoperative pain after cardiac surgery via median sternotomy using analgesic, anaesthetic or surgical interventions.

**DATA SOURCES** PubMed, Embase and Cochrane Databases.

**RESULTS** Of 319 eligible studies, 209 randomised controlled trials and three systematic reviews were included in the final analysis. Pre-operative, intra-operative and postop-

erative interventions that reduced postoperative pain included paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), intravenous magnesium, intravenous dexmedetomidine and parasternal block/infiltration.

**CONCLUSIONS** The analgesic regimen for cardiac surgery via sternotomy should include paracetamol and NSAIDs, unless contraindicated, administered intra-operatively and continued postoperatively. Intra-operative magnesium and dexmedetomidine infusions may be considered as adjuncts particularly when basic analgesics are not administered. It is not clear if combining dexmedetomidine and magnesium would provide superior pain relief compared with either drug alone. Parasternal block/surgical site infiltration is also recommended. However, no basic analgesics were used in the studies assessing these interventions. Opioids should be reserved for rescue analgesia. Other interventions, including cyclo-oxygenase-2 specific inhibitors, are not recommended because there was insufficient, inconsistent or no evidence to support their use and/or due to safety concerns.

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## KEY POINTS

- PROSPECT recommendations for postoperative analgesia for sternotomy were described.
- Paracetamol and NSAIDs intra-operatively and postoperatively are recommended.
- Intra-operative magnesium and dexmedetomidine are useful adjuncts.
- Parasternal block is also recommended.
- Opioids should be used for rescue.

## Introduction

Pain after median sternotomy can be difficult to treat.<sup>1</sup> Poorly controlled postsurgical pain can be debilitating.<sup>2</sup> Furthermore, inadequately managed pain may result in increased postoperative pulmonary complications, cardiac complications (e.g. infarction, arrhythmias) and long-term complications such as poststernotomy pain syndrome.<sup>3,4</sup> Opioids have been the cornerstone for cardiac anaesthesia and analgesia.<sup>5</sup> However, these drugs come with undesirable side effects, including respiratory depression, postoperative nausea and vomiting (PONV), and ileus. This concern has led to efforts towards a multimodal approach to pain management. Several systemic analgesics and regional analgesic techniques have been investigated with variable results regarding their efficacy and safety.<sup>2</sup> However, there are no specific recommendations for pain management after cardiac surgery via median sternotomy.

The PROSPECT (procedure-specific postoperative pain management) Working Group is a collaboration of surgeons and anaesthetists working to formulate procedure-specific recommendations for pain management after common but potentially painful operations.<sup>6</sup> These recommendations are based on a procedure-specific systematic review of randomised controlled trials (RCTs). The methodology considers clinical practice, efficacy and adverse effects of analgesic techniques.<sup>7</sup>

The aim of this systematic review was to evaluate the available literature on the effects of analgesic, anaesthetic and surgical interventions on pain after cardiac surgery via median sternotomy. The primary outcome was postoperative pain scores. Other outcomes, including opioid requirements and adverse effects, were also assessed when reported. Limitations of the data were reviewed. The ultimate aim was to develop recommendations for pain management after cardiac surgery via median sternotomy.

## Materials and methods

This review adhered to the PROSPECT methodology.<sup>8</sup> Specific to this study, the Embase, PubMed and Cochrane Databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts or

Reviews of Effects, Cochrane Database of Systematic Reviews) were searched for all RCTs and systematic reviews published until November 2020. The following search terms were used: sternotom\* OR CABG OR coronary artery bypass OR valve surgery OR cardiac surgery OR heart surgery NOT minimally invasive OR thoracotom\* OR thoracoscop\* AND pain management OR postoperative pain OR postoperative pain OR acute pain OR analgesia OR anaesthesia OR anaesthesia OR vas OR visual analogue score OR vrs OR verbal rating scale OR nrs OR numerical rating scale OR pain rating OR epidural OR neuraxial OR intrathecal OR paravertebral OR erector spinae plane block OR spinal OR infiltration OR nerve block OR neural block OR field block OR NSAID OR nonsteroidal anti-inflammatory OR nonsteroidal anti-inflammatory OR cyclo-oxygenase (COX)-2 OR paracetamol OR acetaminophen OR THC OR marijuana OR tetrahydrocannabinol OR clonidine OR dexmedetomidine OR opioid OR ketamine OR corticosteroid OR gabapentin OR pregabalin OR TENS OR electrotherapy OR pain intensity OR dipyrrone OR nefopam OR PCA OR patient controlled analgesia OR morphine OR piritramide OR PCIA AND RCT OR randomised controlled OR systematic review OR randomized controlled trial OR systematic review NOT paediatric OR paediatric OR child\*.

Data extraction and data analysis adhered to the PROSPECT methodology.<sup>8</sup> Pain intensity scores were used as the primary outcome measure. A change of more than 10 mm on the 100 mm visual analogue scale (VAS) or 1 in the 0 to 10 numerical rating score (NRS) was considered clinically relevant. A meta-analysis was not performed due to the heterogeneity in study designs and results reporting restricting a pooled analysis.

Recommendations were made according to the PROSPECT methodology.<sup>7,8</sup> The proposed recommendations were sent to the PROSPECT Working Group for review and comments and a modified Delphi approach was utilised as previously described. Once a consensus was achieved, the lead authors drafted the final document, which was ultimately approved by the working group.

## Results

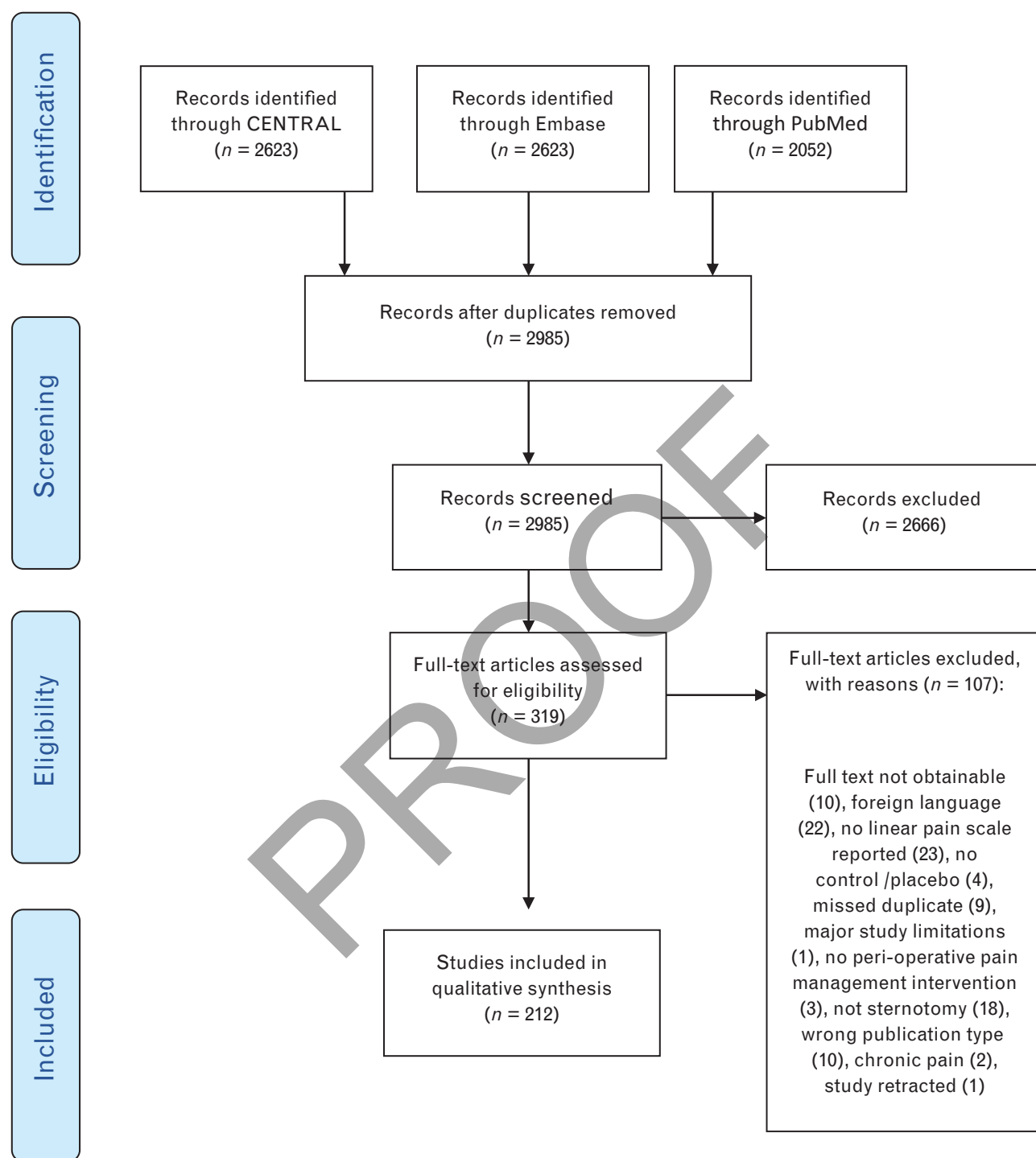
The PRISMA flow chart presenting the search data is presented in Fig. 1. Studies which were reviewed but not mentioned in the text are listed in Supplementary Table S1, <http://links.lww.com/EJA/A855>. The characteristics of the included studies are shown in Supplementary Tables S2, <http://links.lww.com/EJA/A856> and S3, <http://links.lww.com/EJA/A857>.

## Systemic analgesics

### Paracetamol

Mamoun *et al.*<sup>9</sup> recorded a statistically significant improvement in pain scores with paracetamol postoperatively compared with placebo, with no significant reduction

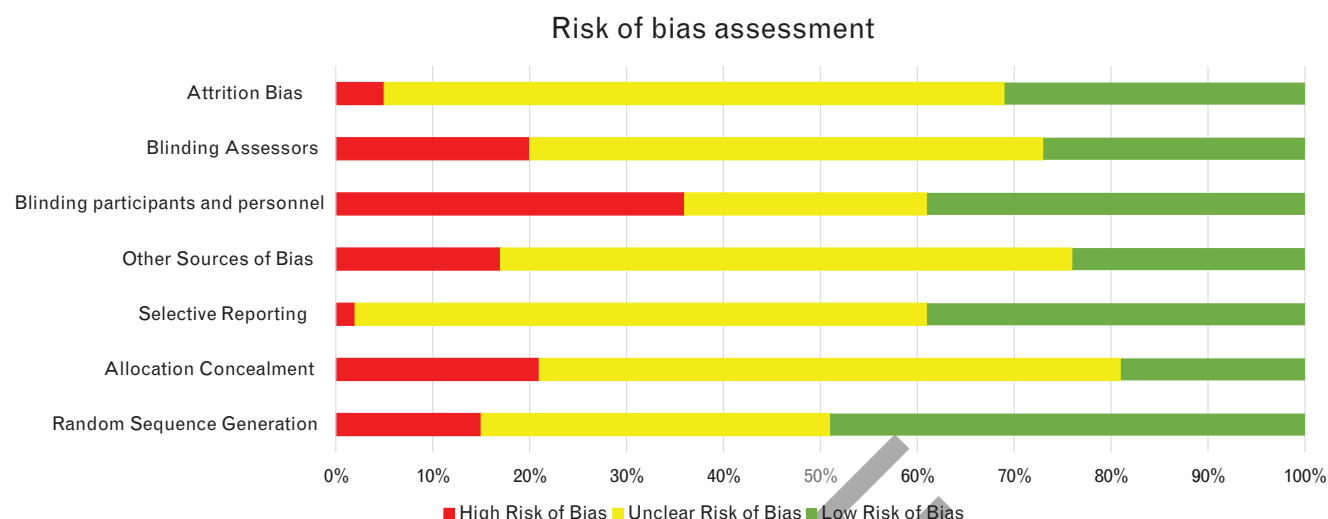
Fig. 1 PRISMA flow chart of studies.



in opioid consumption. Douzjian and Kulik<sup>10</sup> conducted a meta-analysis of randomised clinical trials assessing paracetamol: nine studies were included, and of these, three reported a lower opioid consumption, improved pain control and improved pulmonary function early after surgery. However, two larger clinical trials involving intravenous (i.v.)

paracetamol in combination with rescue opioids recorded only a marginal improvement in pain scores during the first 24 h. Arslan *et al.*<sup>11</sup> observed significantly lower pain scores at 12 h with paracetamol given every 6 h postoperatively compared to placebo. Overall, paracetamol is recommended as a part of basic analgesia ().

**Fig. 2** Summary of the risk of bias assessment in which for each item of the Risk of Bias tool the percentage of included studies with high, low and unclear risk was given.



### NSAIDs and COX-2 specific inhibitors

Rapanos *et al.*<sup>12</sup> compared 100 mg rectal indomethacin to placebo postoperatively and recorded a significant reduction in opioid consumption and pain scores in the first 24 h. No major adverse events were reported. Daglar *et al.*<sup>13</sup> studied 40 patients who received either lornoxicam 8 mg intramuscular (i.m.) every 8 h or diclofenac 75 mg i.m. every 12 h for 48 h in a single-blind design. They found no significant differences in pain scores at all time points. Both drugs were well tolerated with absence of gastric discomfort, nausea, vomiting, hypotension, bradycardia or renal failure. Opioid consumption was not reported. Ott *et al.*<sup>14</sup> reported significantly reduced pain scores and morphine consumption with i.v. parecoxib followed by oral valdecoxib compared with placebo. However, they noted a higher incidence of serious adverse events and sternal wound infections at 14 days in those receiving COX-2 inhibitors continuously for 14 days. Dhawan *et al.*<sup>15</sup> reported significantly lower pain scores in the first 6 h after surgery and a 40% reduction in opioid consumption with 100 mg of rectal diclofenac compared with placebo. Eljezi *et al.*<sup>16</sup> found that ketoprofen 0.5 mg kg<sup>-1</sup> significantly reduced dynamic and static pain compared with lower doses of 0.25 and 0.125 mg kg<sup>-1</sup>. Immer *et al.*<sup>17</sup> compared tramadol 150 mg every 12 h, diclofenac 50 mg every 8 h and etodolac 300 mg every 8 h. Significantly lower pain scores were recorded in the etodolac group from postoperative day (POD) 2 to 4 compared with the tramadol group. The diclofenac group reported lower pain scores than the tramadol group only on PODs 3 and 4. All other pain-related outcomes including opioid use were similar. In a placebo-controlled study, Koizuka *et al.*<sup>18</sup> found lower pain scores with etodolac 400 mg via a nasogastric tube at

the end of surgery. Opioid consumption did not differ significantly. Kulik *et al.*<sup>19</sup> demonstrated a significant reduction in pain scores of patients receiving rectal naproxen (500 mg 1 h postoperatively, then every 12 h for five doses followed by 250 mg every 8 h for six doses). There was no significant difference in opioid consumption. No adverse events were reported. Maddali *et al.*<sup>20</sup> compared continuous fentanyl i.v. infusion intra-operatively and postoperatively, fentanyl bolus doses intra-operatively and diclofenac suppository postoperatively, and continuous i.v. infusion of remifentanyl intra-operatively and i.v. fentanyl as an immediate postoperative bolus followed by continuous fentanyl infusion. There were no significant differences in pain scores across the groups. The diclofenac group exhibited the shortest time to extubation, the least inotrope use and the fewest rescue doses of analgesic compared with the other two groups. Overall, NSAIDs are recommended as basic analgesics postoperatively. In contrast, COX-2 specific inhibitors cannot be recommended due to lack of evidence and safety concerns.<sup>14,21</sup>

### Dexmedetomidine

Abdel-Meguid<sup>22</sup> compared dexmedetomidine infusion or placebo intra-operatively, continued up to 12 h postoperatively. Dexmedetomidine reduced time to extubation, opioid use and pain scores. In a study by Hashemian *et al.*,<sup>23</sup> dexmedetomidine 0.5 µg kg<sup>-1</sup> h<sup>-1</sup> given from the initiation of anaesthesia until tracheal extubation in the ICU reduced pain scores and opioid use compared with placebo. Priye *et al.*<sup>24</sup> observed that dexmedetomidine significantly reduced postoperative pain scores, opioid consumption and delirium without influencing haemodynamic parameters. Aziz *et al.*<sup>25</sup> randomised 28 patients

to receive either dexmedetomidine or morphine. They found no significant differences between the two groups for the outcome measures except for heart rate, which was significantly lower in the dexmedetomidine group. Anvaripour *et al.*<sup>26</sup> found that dexmedetomidine or morphine administered as i.v. patient-controlled analgesia resulted in similar demands for rescue opioids, sedation levels, PONV and haemodynamic profiles. It is noteworthy that no basic analgesia (i.e. paracetamol and/or NSAIDs) was used in any of these studies. Thus, intra-operative dexmedetomidine i.v. infusion may be used, particularly when basic analgesics are not administered or are contraindicated.

### Magnesium

Ahmad *et al.*<sup>27</sup> reported lower pain scores with intra-operative magnesium (2 g bolus and 2 g 70 kg<sup>-1</sup> day<sup>-1</sup>) compared with codeine and diclofenac. Bolcal *et al.*<sup>28</sup> observed superior pain scores and lower morphine use with magnesium. In a placebo-controlled study, Ferasatkish *et al.*<sup>29</sup> observed that intra-operative magnesium reduced pain scores and opioid use as well as shortening the time to extubation. Of note, two patients experienced extreme bradycardia and hypotension and were excluded from analysis. Alavi *et al.*<sup>30</sup> found that magnesium i.v. significantly reduced opioid use and pain scores at all time points, although these results were not clinically relevant. Another study reported that magnesium infusion for 12 h postoperatively reduced pain scores without a reduction in postoperative analgesic requirements.<sup>31</sup> Of note, no basic analgesia (i.e. paracetamol and/or NSAIDs) was used in any of these studies. Overall, intra-operative magnesium i.v. infusion may be used, particularly when basic analgesics are not administered or are contraindicated.

### Systemic opioids

Ruetzler *et al.*<sup>32</sup> compared oral Targin (a combination of oxycodone and naloxone) with patient-controlled i.v. morphine and observed lower opioid consumption with the oral opioid without significant differences in pain scores. Kogan *et al.*<sup>33</sup> compared the 6-hourly administration of an immediate release combination of oxycodone 5 mg and paracetamol 325 mg with controlled-release oxycodone 10 mg given every 12 h and placebo for blinding. Pain scores and rescue analgesia were lower in the immediate release combined group. Overall, there is no evidence to support one opioid over the other. Opioids should be reserved as rescue analgesia postoperatively.

### Ketamine

Cameron *et al.*<sup>34</sup> found no difference in pain scores and opioid use when ketamine (0.5 mg kg<sup>-1</sup> i.v. bolus before skin incision, followed by an infusion of 0.5 mg kg<sup>-1</sup> h<sup>-1</sup> until the end of surgery) was compared with placebo. Lahtinen *et al.*<sup>35</sup> also found no significant differences in pain scores and opioid consumption with intra-operative

S (+) ketamine versus placebo. Overall, intra-operative ketamine is not recommended.

### Loco-regional techniques

#### Parasternal block/infiltration

Three studies<sup>36–38</sup> evaluated the effects of a parasternal block with local anaesthetic compared with a standardised regimen and observed a reduction in pain scores and postoperative opioid requirement. The injected solutions differed between the trials. The parasternal block was compared with a placebo (injected normal saline 0.9%) in two studies.<sup>39,40</sup> These found a significant opioid-sparing effect, but only Barr *et al.*<sup>39</sup> observed significantly lower pain scores. The use of liposomal bupivacaine for the parasternal block did not show any significant difference for pain scores or opioid consumption.<sup>41</sup> Overall, intra-operative parasternal block/infiltration is recommended. Unfortunately, parasternal block was only studied in investigations in which no basic analgesia was administered.

#### Paravertebral block

Paravertebral block showed reduced pain scores and opioid consumption compared with a control group in two studies.<sup>42,43</sup> However, the pain reduction was not significant in one of the studies.<sup>42</sup> In another study, neither pain scores nor opioid consumption was significantly reduced compared with thoracic epidural analgesia (TEA).<sup>44</sup> Paravertebral block is thus not recommended for analgesia after sternotomy.

#### Transversus thoracic muscle plane block

In the pilot feasibility study, bilateral transversus thoracic muscle plane block significantly reduced pain scores at 12 h after surgery.<sup>45</sup> There was no reduction in opioid consumption.

#### Erector spinae plane block

Krishna *et al.*<sup>46</sup> compared a single shot erector spinae plane block on top of basic analgesia (paracetamol and tramadol) and observed a significant reduction in pain scores and opioid consumption. Nagaraja *et al.*<sup>47</sup> compared the ESP block with TEA, both with continuous infusion for 48 h. ESP block was noninferior to the TEA in the first 12 h. The use of ESP block cannot be recommended due to limited evidence.

#### Epidural analgesia and intrathecal opioids

Twenty RCTs involving intrathecal anaesthesia were included in our systematic review. Two studies<sup>48,49</sup> compared the effect of intrathecal morphine with placebo and observed a reduction in opioid consumption. Reduction in pain scores was at 2 and 4 h postoperatively in the study of Jacobsohn *et al.*<sup>49</sup> Four studies compared intrathecal opioid administration with a subcutaneous sham injection with 0.9% saline<sup>50,51</sup> or local anaesthetic.<sup>52,53</sup> Three studies observed a significantly reduced opioid



consumption in the intervention group except in the study of Mehta *et al.*<sup>51</sup> wherein i.v. tramadol ( $1.5 \text{ mg kg}^{-1}$ ) was given every 8 h as baseline analgesia. Pain scores were significantly better with use of intrathecal morphine in three studies.<sup>52–54</sup> Roediger *et al.*<sup>52</sup> observed a reduction in pain scores at rest but not during coughing. Pain scores were not significantly different in the study by Boulanger *et al.*<sup>50</sup> Twelve studies<sup>55–66</sup> compared intrathecal opioid (preservative free morphine alone or combined with sufentanil or fentanyl in two studies<sup>55,65</sup> or combined with clonidine in two studies<sup>64,66</sup>) with a routine treatment (i.v. opioids). All observed a significant reduction in opioid consumption in the intervention group. Eight studies observed a clinically and statistically significant reduction in pain scores.<sup>57,58,60–64,66</sup> Two studies<sup>67,68</sup> compared the effect of intrathecal clonidine as an adjunct versus intrathecal morphine alone and observed both a significant analgesic and an opioid sparing effect with the addition of clonidine. Side effects and complications of intrathecal anaesthesia were rarely observed. No spinal haematoma was reported. Pruritus, nausea and vomiting were reported in some studies<sup>53,59,63</sup> but were easily managed with diphenhydramine and antiemetics, respectively. Two studies<sup>59,63</sup> reported postdural puncture headache (PDPH) and bradypnoea.

The meta-analysis by Guay and Kopp,<sup>69</sup> which included 69 trials with 4860 patients given epidural analgesia and 2456 receiving comparators (systemic analgesia, peripheral nerve block, intrapleural analgesia or wound infiltration), found insufficient evidence to show clear benefits of epidural analgesia compared with peripheral nerve blocks, intrapleural analgesia or wound infiltration. There was a small reduction in the risk of respiratory depression but not pneumonia with epidural pain relief. No lasting neurological complications or epidural haematomas were reported, but the quality of evidence was low to very low, according to Cochrane standards.

In the meta-analysis by Zhang *et al.*,<sup>70</sup> nine studies reported on the effects of epidural analgesia on pain scores. Patients who received TEA and general anaesthesia had significantly lower pain scores than general anaesthesia alone. The prevalence of respiratory complications was significantly reduced in the TEA group. Neurological events were not reported. In the study by Tenenbein *et al.*,<sup>71</sup> TEA significantly improved pain scores but not opioid consumption. Rectal indomethacin 100 mg or naproxen 500 mg were administered every 12 h. El-Morsy and El-Deeb<sup>72</sup> investigated the effect of TEA as an adjunct to general anaesthesia. No significant reduction in pain scores was observed. Opioid consumption was significantly reduced. No basic analgesia was used.

In a placebo-controlled study by Onan *et al.*,<sup>73</sup> TEA in comparison with no TEA significantly reduced opioid consumption and reduced the intensity of postoperative pain. Sharma *et al.*<sup>74</sup> demonstrated better analgesia,

earlier tracheal extubation and a shorter ICU stay in obese patients receiving TEA compared with a tramadol infusion. There were no complications related to the thoracic epidural.

Although it is generally accepted that epidural analgesia and intrathecal opioids provide excellent pain relief and reduce opioid use, two meta-analyses<sup>69,70</sup> could not prove a clear benefit with regards to analgesia and opioid consumption. Nevertheless, epidural analgesia with or without opioids and/or intrathecal opioids cannot be recommended due to safety concerns in patients treated with a high dose of anticoagulants.

### **Surgical site local anaesthetic infusion**

One study<sup>75</sup> over 48 h combined a bilateral intercostal nerve block with a parasternal wound infusion using either ropivacaine 0.2% or placebo; significantly lower pain scores and opioid consumption were observed in the intervention group. A second study,<sup>76</sup> also over 48 h, compared presternal wound infusion with either bupivacaine 0.25 or 0.9% saline and again observed significantly lower pain scores and opioid consumption in the intervention group. Six studies<sup>77–82</sup> compared local anaesthetic wound infiltration through a catheter using either local anaesthetic or 0.9% saline. Of these, three studies<sup>77,80,81</sup> showed no significant difference in pain scores or opioid consumption. The two smaller studies<sup>78,79</sup> observed a reduction in pain scores and opioid consumption. Eljezi *et al.*<sup>78</sup> observed an opioid-sparing effect of bupivacaine 0.5% compared with bupivacaine 0.25% or placebo. Kamel *et al.*<sup>82</sup> compared infusions of either a bupivacaine magnesium mixture, or bupivacaine alone, or 0.9% saline. Only the 0.9% saline group received conventional baseline analgesics (paracetamol and ketorolac). Pain scores were statistically lower in the bupivacaine and magnesium group compared with the other two groups. Total rescue fentanyl consumption was reduced in the bupivacaine group and even more in the bupivacaine and magnesium group compared with the control group. Eljezi *et al.*<sup>83</sup> compared local sternal infusion with 0.2% ropivacaine with standard care and observed better dynamic pain scores but no difference in opioid consumption. Kocabas *et al.*<sup>84</sup> compared a single local infiltration (60 ml 0.25% levobupivacaine) of the sternotomy wound and mediastinal tube wounds with placebo (60 ml 0.9% saline) and observed a significant opioid sparing effect without a difference in pain scores. Magnano *et al.*<sup>85</sup> found no statistical difference between a parasternal infiltration with 10 ml of bupivacaine 0.5% and a continuous infusion through a catheter. Thus, the use of regional analgesia with surgeon administered parasternal block/infiltration is recommended.

### **Nonpharmacological interventions**

Two studies<sup>86,87</sup> investigated the effect of massaging the patient's hands on postoperative pain and found

significantly improved pain scores compared with placebo (i.e. simply holding the patient's hands, or resting). Other studies, foot massage,<sup>88,89</sup> Swedish massage,<sup>90</sup> individualised massage<sup>91</sup> and general massage<sup>92</sup> observed improvement in short-term pain scores. Mitchinson<sup>93</sup> found similar results; however, objectively measured outcomes, such as analgesic requirements, length of hospital stay and functional recovery were not universally reported.

Four RCTs analysed the effect of music therapy after sternotomy and observed reduced pain scores in all trials. There was no reduction in opioid consumption.<sup>94,95</sup> The control groups received a period of rest<sup>94–96</sup> or headphones without music.<sup>96</sup>

Postoperative pain education with a booklet<sup>97</sup> or short face-to-face explanation<sup>98</sup> could not produce a clinically significant improvement in pain scores or opioid consumption. Pain scores and opioid consumption did not improve significantly with pre-operative pain education.<sup>97–99</sup> Martorella *et al.*<sup>100</sup> observed even more opioid consumption in the intervention group. In one study, a full day of pre-operative education was studied, with no discernible difference in primary outcomes from normal care.<sup>101</sup>

Overall, massage therapy and music therapy are recommended as adjuncts to pharmacological interventions.

### Surgical techniques

Several surgical techniques were employed, including skeletonisation, sutures and wound closure techniques, pleurotomy, chest tube position and corset. Analgesic protocols and use of basic analgesics were inconsistently reported making it impossible to recommend any specific surgical technique.

### Discussion

This study critically evaluated the available evidence for analgesic interventions in patients undergoing cardiac surgery via median sternotomy. Unlike previous reviews that looked at individual analgesic interventions (e.g. regional analgesic techniques<sup>2</sup>), this is the first to evaluate all possible analgesic interventions. On the basis of the available evidence and the PROSPECT approach to providing recommendations, combinations of paracetamol and an NSAID are recommended pre-operatively or intra-operatively, and should be continued into the postoperative period, unless there are contra-indications. However, COX-2 specific inhibitors could not be recommended due to lack of evidence and safety concerns (more wound infections after 14 days of continuous use). Although NSAIDs have been shown to be highly efficacious in reducing pain and opioid requirements, they are commonly avoided in the peri-operative period due to concerns of potential adverse effects such as cardiovascular

injury,<sup>102</sup> renal dysfunction and bleeding.<sup>103</sup> However, recent evidence on NSAID-related increased adverse events indicates that this is related to their prolonged use at higher doses and/or in inappropriate patient groups. It is suggested that the risk of acute kidney injury or increase in the incidence cardiac adverse events with a short duration of use after cardiac surgery is low.<sup>104</sup> Despite boxed warnings cautioning against NSAID use after cardiac surgery, short courses of non-selective NSAIDs may be relatively well tolerated in this patient group.<sup>104</sup> Similarly, a recent systematic review questioned the concerns of NSAID-induced bleeding.<sup>105</sup>

Dexmedetomidine, a highly selective  $\alpha_2$ -adrenergic receptor agonist, is known to have features, including analgesia, anxiolysis and sedation. Activation of  $\alpha_2$  receptors induce a central inhibition of sympathetic stimulation that results in analgesia and therefore less opioid consumption. Dexmedetomidine is also associated with improved outcomes after cardiac surgery.<sup>101</sup> Although the studies included in this systematic review reported reduced pain scores and opioid requirements, basic analgesics were not administered. Thus, intra-operative dexmedetomidine infusion may have a role in patients undergoing cardiac surgery, particularly when basic analgesics are not administered or contraindicated. One of the major concerns with dexmedetomidine is the associated prolonged bradycardia and hypotension, which may extend into the postoperative period.<sup>106</sup> In one study, two patients experienced extreme bradycardia and hypotension.<sup>29</sup> Also, dexmedetomidine can cause airway obstruction, and increase the risk of postoperative hypoxia.<sup>107</sup>

Magnesium is often used in cardiac surgery for its antiarrhythmic properties. Studies included in this systematic review found reduced pain scores and opioid requirements with the use of magnesium; however, basic analgesics were not used. Similar to dexmedetomidine, magnesium can potentiate hypotensive effects of other adjuncts and potentiate neuromuscular blockade and increase the risk of residual paralysis.<sup>108</sup> Therefore, careful consideration is needed when using dexmedetomidine and magnesium, particularly in the patients at risk of haemodynamically instability. Importantly, it is not clear if combining dexmedetomidine and magnesium would provide superior pain relief compared with either drug alone. Furthermore, optimal combination of these agents or their dosing remains unclear.<sup>109</sup>

In addition to basic analgesics, the use of regional analgesia with surgeon administered parasternal block/infiltration is recommended. However, despite well described analgesic efficacy of epidural analgesia and intrathecal opioids,<sup>69,70</sup> these techniques are not recommended due to concerns of potential adverse events.<sup>110</sup> Despite the limitations in the study design, nonpharmacological interventions such as music therapy and massage therapy are

recommended as adjuncts to pharmacological therapy. These approaches have the potential to enhance the analgesic effects of pharmacologic interventions without inducing any harm.

Pain after sternotomy can be categorised as moderate, especially when compared with other types of surgical approaches to the thorax.<sup>111</sup> Clinicians should be alert to the fact that the intensity of pain related to chest tubes can be more debilitating than the actual pain of the sternotomy.<sup>112,113</sup> Chest tubes are usually placed during sternotomy, and therefore, pain generated by these should also be managed by our recommendations. In most studies, chest tubes were present. Furthermore, pain after sternotomy does not only involve the actual sternotomy, but also the pain related to other aspects of surgery such as the internal mammary dissection.

The PROSPECT recommendations do not consider chronic postsurgery pain that occurs relatively frequently in this patient group. Up to 17% of patients have persistent pain for more than 6 months after surgery.<sup>114</sup> Specific interventions directed at prevention of persistent pain in patients at high risk might be employed on top of our recommendations.

The present study suffers limitations inherent to the included studies. Newer regional analgesic techniques such as ESP block could not be recommended due to insufficient or limited evidence, but future positive studies may modify our recommendations. The role of ESP blocks has been expanding, with reports of good analgesic efficacy and the ability to use these blocks in patients receiving antithrombotic therapy.<sup>111</sup> Also, challenging patient groups at a high risk of postoperative persistent pain, such as after cardiac surgery, have not been studied, and thus, specific analgesic therapy for these patients could not be developed. Importantly,

**Table 1** Overall recommendations for peri-operative pain management in patients undergoing cardiac surgery via median sternotomy

Intra-operative
Paracetamol and NSAIDs (if no contraindications)
Consider dexmedetomidine, intravenous infusion, as adjunct particularly when basic analgesics are not administered
Consider magnesium, intravenous infusion, as adjunct particularly when basic analgesics are not administered
Parasternal block/surgical wound infiltration
Nonpharmacological therapy such as music and massage, as adjunct to pharmacologic therapy
Postoperative
Paracetamol and NSAIDs (if no contra-indications)
Opioids as rescue analgesia

administration of basic analgesics (i.e. NSAIDs combined with paracetamol) was missing in many studies, and this precludes an objective evaluation of the benefits of the analgesic interventions such as dexmedetomidine and magnesium. Of note, in many studies, pain scores were improved with the studied intervention, but this did not always result in lower opioid consumption. The absence of ‘basic’ analgesia might be related to this effect.

In summary, the present study identified an optimal analgesic regimen for patients undergoing elective cardiac surgery via median sternotomy (Table 1). Analgesic interventions that could not be recommended were also identified (Table 2). Future studies should include basic analgesics as a component of multimodal analgesia in all the study groups; this is necessary to confirm that the analgesic intervention being investigated actually has additional analgesic benefits. Future studies should focus on the effects of analgesic interventions for fast-track cardiac surgery, including the ability to allow early tracheal extubation and early ambulation.

**Table 2** Interventions that are not recommended for pain management in patients undergoing cardiac surgery via median sternotomy

Interventions	Reasons for not recommending
Cyclo-oxygenase-2 specific inhibitors	Limited procedure-specific evidence and safety concerns
Gabapentinoids	Inconsistent procedure-specific evidence
Ketamine	Lack of procedure-specific evidence
Epidural analgesia	Inconsistent evidence, safety concerns
Intrathecal opioids	Inconsistent evidence, safety concerns
Lidocaine infusion	Lack of procedure-specific evidence
Nefopam	Lack of procedure-specific evidence
Methadone	Limited procedure specific evidence
Kinesio tape	Limited procedure-specific evidence
Pre-operative physiotherapeutic instructions	Lack of procedure-specific evidence
Acupuncture	Limited procedure-specific evidence
Classical chest physiotherapy	Lack of procedure-specific evidence
Hypnosis	Limited procedure-specific evidence
Aromatherapy (lavender oil)	Lack of procedure-specific evidence
Reiki	Lack of procedure-specific evidence
Psychological interventions	Limited procedure-specific evidence
Early extubation	Lack of procedure-specific evidence



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