ABSTRACT

AIM: To synthesise the best available empirical evidence about the effectiveness of multimodal analgesics on pain after adult cardiac surgery.

DESIGN: A systematic review with meta-analysis.

METHODS: Indexed full-text papers or abstracts, in any language, of randomised controlled trials of adult patients undergoing cardiac surgery investigating multimodal postoperative analgesic regimen effect on mean level of patient reported pain intensity at rest.

DATA SOURCES: Eight databases, via two platforms and three trial registries were searched from 1st January 1995 to 1st of June 2024 returning 3823 citations.

RESULTS: Of the 123 full-text papers assessed 29 were eligible for inclusion. Data were independently extracted by a minimum of two reviewers in Covidence®. There were 2195 participants, aged 60.4 ± 6.6 (Range 40-79) years, who were primarily male (n = 1522, 76.1%), randomised in the included studies. Risk of bias was high and reporting quality was poor. Patient reported pain was measured at rest in 28 (96.6%) trials. Data were suitable for pooled analysis from 10 (34.5%) of these trials with an average rest pain intensity of 3.3 (SD 1.5) in the control and 2.7 (SD 1.9) in the intervention groups respectively. No trials compared combinations of non-opioid, opioid-agonist-antagonist, partial opioid agonists or full opioid agonists. Most trials (n = 11, 37.9%) compared two different full opioid options for less than 72 hours (n = 24, 82.7%).

CONCLUSIONS: Robust trials are needed to determine which multimodal analgesic combination will optimise patient recovery after adult cardiac surgery. There is an urgent need to test and refine high quality end point measures.

Implications for patient care: Adequate assessment precedes ideal pain treatment. The findings from this review reveal neither are sufficient and the impact of sub-optimal pain management on postoperative recovery is grossly under-investigated.

Impact.

The optimal combination of multimodal analgesics is unknown despite being recommended in best practice guidelines for enhanced recovery after cardiac surgery. Almost 30% of adults continue to experience ongoing pain up to a year after cardiac surgery, and findings from this review reveal a dearth of robust empirical evidence for optimal pain management, and heterogeneity in the way pain is assessed, measured and managed. This review provides a premise for robust trials focused on acute postoperative recovery in cardiac surgery and beyond.

This review was conducted in accordance with the PRISMA-P statement.

There was no patient or public contribution.

Keywords: Pain, Cardiac Surgery, Analgesic, Postoperative, Systematic Review

What this paper contributes to the wider global community.

- Findings from this review reveal sub-optimal evidence for pain management during the acute postoperative recovery after adult cardiac surgery.
- The evidence indicates poor quality trials, with high risk of bias and incomplete reporting.
- There was significant heterogeneity in randomised controlled trials in terms of analgesic combinations tested, pain related endpoint measurement and patient related outcome measures.

Protocol Registration: (PROSPERO: CRD[redacted]).

INTRODUCTION

Protocols for enhanced recovery after surgery-cardiac surgery (ERAS CS) provide a fast-track framework for preoperative and intraoperative care (Engelman et al., 2019). Significant reductions in hospital length of stay are attributed to ERAS CS (Hoyler et al., 2020), yet the postoperative length of stay interval has remained relatively consistent for more than a decade (Wong et al., 2016). There is a plethora of research exploring regional anaesthesia (Svircevic et al., 2013), or the combination of analgesia administered during anaesthesia and while cardiac surgical patients remain intubated and mechanically ventilated in the intensive care unit (ICU) (Kehlet & Joshi, 2015). Once transferred from the ICU to high-dependency or acute care services, the volume of research that investigates the effectiveness of multi-modal analgesia diminishes. Multi-modal, opioid sparing analgesic approaches are emphasised in the literature but robust evidence describing the optimal combination of these medications for adults undergoing cardiac surgery is scant (Ochroch et al., 2021).

In contrast, numerous observational cohort studies report substantial proportions of patients experiencing moderate to severe pain in the first few days after surgery, with 30% reporting persistent pain up to a year after surgery (Bjørnnes, Parry, et al., 2016; Gjeilo et al., 2014), where poorly managed postoperative pain increases the risk of ongoing chronic pain (Choinière et al., 2014). Randomised controlled clinical trials (RCT) testing the effectiveness of multi-modal analgesics on patient reported outcomes have not been used to inform the development of ERAS CS protocols (Wynne et al., 2024). The purpose of this systematic review was to collate and synthesise evidence of multi-modal analgesic effectiveness for postoperative pain management following ICU discharge, in adults having cardiac surgery. Specific objectives of this review were to i) identify combinations of postoperative analgesics; ii) assess whether these were multi-modal; iii) examine the ratio of prescribed to administered analgesics; and iv) determine which multi-modal combination was the most effective on patient reported pain management and length of stay.

METHODS

Design

The protocol for this systematic review was registered with the Prospective Register of Systematic Reviews ([redacted]), and review findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols Statement (Page et al., 2021). Review methods were designed to align with the procedure-specific pain management (PROSPECT) initiative (Joshi et al., 2019). The protocol for this review has been published elsewhere [redacted] which detailed information describing information sources, the search strategy, and data management. The search of publications from 1995 to the 1st of June 2024 was conducted and reference management software Endnote® was used to collate search findings that were subsequently imported into Covidence® for the removal of duplicates, screening, and selection.

Inclusion Criteria

The population of interest was adult patients (≥ 18 years of age) undergoing cardiac surgery (coronary artery bypass grafting, valvular replacement or repair, repair or replacement of the thoracic aorta involving the aortic valve, neoplasm resection, and repair of congenital lesions) via median sternotomy with or without cardiopulmonary bypass. There were no time or language restrictions on the search.

Types of Studies.

Primary RCT with parallel group, factorial, crossover, or cluster designs were included along with systematic reviews of RCTs reported in indexed full-text articles or published abstracts with adequate information reported.

Types of Interventions.

Interventions of interest involved the administration of multi-modal analgesics. Analgesics were indexed according to potency: full or partial opioid agonists, opioid agonist-antagonist agents,

and non-opioids. Interventions had to be initiated or continue during the postoperative recovery trajectory interval which could include the intensive care unit (ICU), high dependency unit or acute recovery ward. Analgesics of interest were administered systemically via enteral, parenteral, intravenous, intramuscular, or sub-cutaneous injection routes. The comparator of interest was standard care or usual analgesic administration.

Types of Outcome.

The primary outcome measure was 24-hourly patient-reported pain intensity at rest and/or during activity to align with PROSPECT (Joshi et al., 2019) recommendations. Pain intensity was captured using validated subjective assessment tools such as the visual analogue or numerical rating scale. Secondary outcome measures were type of analgesic, ratio of prescribed to administered analgesic, mean dose of each type of analgesic administered, time to first rescue analgesic, cumulative 24-hour analgesic requirements, intervention-related adverse events, and hospital length of stay (days).

Exclusion Criteria

Studies that were non-experimental or focused on animal or paediatric samples were excluded. Reports that included patients having surgery for ventricular device insertion, extracorporeal membrane oxygenation, heart or lung transplantation, trans-catheter device insertion or minimally invasive approaches were also excluded. Studies designed to test the effect of regional anaesthesia as an adjunct to multimodal analgesia were not considered relevant. Similarly, studies in which the intervention was implemented as a component of anesthetic induction or ceased prior to the postoperative interval commencing (in the operating room, recovery unit or ICU) were excluded. Journals that were not indexed and non-peer reviewed sources of literature were excluded.

Data Extraction & Quality Assessment

Two reviewers independently screened citation title and abstracts ([redacted]), with a third available for consensus moderation ([redacted]). Full-text screening, data extraction and quality assessment were completed by two leads ([redacted]) each working with three co-authors. Data extraction was completed in Covidence® using a modified version of the Covidence® extraction template. We extracted data reporting study and patient characteristics, operative details, intervention and control group analgesics, analgesic type (non-opioid, opioid-agonist-antagonist, full opioid), dose prescribed and administered, route and duration of administration, number of patients completing follow-up, patient reported pain score at rest and with activity, adverse events, and length of stay in ICU and hospital. The final review of extracted data was completed by the two lead reviewers ([redacted]).

The Consolidated Standards of Reporting Trials (CONSORT) (Pandis et al., 2017) checklist for reporting RCT was used to assess methodological and reporting quality of included studies. Instruments used to capture outcome measures were examined for consistency. Two independent reviewers ([redacted]) examined variability in reporting sequence generation, allocation concealment, outcome assessment blinding, incomplete data and selective outcome reporting in the revised Cochrane Collaboration Risk of Bias tool (RoB V2.0). A summary assessment of each domain was generated indicating if specific papers had a ‘low’, ‘unclear’ or ‘high’ risk of bias.

Data Analysis

Study characteristics and endpoint measures for primary and secondary outcomes were extracted in Covidence® then exported into Excel®. A minimum of two trials with comparable outcome measures were necessary for meta-analysis using a random effects model that was a variation of the DerSimonian and Laird method built using standardised mean difference (Hedge’s g) for continuous data in IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Pooled results for the primary outcome are illustrated using forest plots and heterogeneity

assessed using the I^2 statistic was illustrated and interpreted using funnel plots (Sterne et al., 2011). Sensitivity and sub-group analyses were not feasible in the context of minimal descriptive data regarding sample and operative characteristics.

RESULTS

Of 3823 citations identified, there were 1605 duplicates leaving 2218 citations for title and abstract screening, of which 2095 were ineligible. There were 123 full-text papers assessed and 29 were eligible for inclusion (Figure 1). Ineligible papers were primarily related to 'wrong study design' (n = 42) where the study was retrospective or observational and this was not clear in the title and abstract, 'wrong intervention' (n = 23) where analgesic administration was specifically targeting an activity or action such as chest tube removal, or the paper was from a non-peer reviewed (Quartile 4) source (n = 22).

Study Characteristics

Study characteristics for included trials are detailed in Table 1. Most trials took place in countries affiliated with the European Union (n = 8), Turkey (n = 5) or Canada (n = 4) with a relatively even split in publication across decades (between 1994 and 1999 (n = 7) (Boldt et al., 1998; Gust et al., 1999; Munro et al., 1998; Myles et al., 1994; O'Halloran & Brown, 1997; Searle et al.; Tsang & Brush, 1999), 2000 and 2010 (n = 12) (Baltali et al., 2009; Cattabriga et al., 2007; Daglar et al., 2005; Gurbet et al., 2004; Immer et al., 2003; Kogan et al., 2007; Kulik et al., 2004; Lahtinen et al., 2004; Lahtinen et al., 2002; Mota et al., 2010; Pettersson et al., 2000; Rapchuk et al., 2010), or 2011 to 2020 (n = 10) (Altun et al., 2017; Bouzia et al., 2017; Eljezi et al., 2017; Iyer et al., 2015; Javaherforooshzadeh et al., 2020; Lakdizaji et al., 2012; Pesonen et al., 2011; Rafiq et al., 2014; Ruetzler et al., 2014; Tur & Akpek, 2011) . Overall, 2396 participants were recruited and 2195 (91.6%) were randomised with study samples ranging from N = 50 to N = 180 participants.

Quality Assessment & Risk of Bias

Risk of bias was high (n = 16, 55.2%), low (n = 9, 31%) or of some concern (n = 4, 13.8%), generally related to deviations from the intended intervention or unclear outcome measures (Figure 2). Reporting quality was poor with none of the included trials reporting all of the CONSORT checklist items. Single trials reported interim analyses or stopping guidelines. Changes to methods after commencement were clarified in three papers (10.3%), binary outcomes were reported in three papers (10.3%), four papers (13.8%) had accessible protocols and nine (31%) were missing randomisation flow diagrams. Only 6 (20.7%) trials were registered and 10 (34.5%) were supported by funding. Sample size determination was reported in 17 (58.6%) trials, but descriptions were vague with insufficient information for replication. Cross-over was not reported for any trial, nor was early termination in the context of scant data describing recruitment processes in all trials.

Overview of Study Findings

Baseline characteristics are detailed in Table 1. In brief, participants were aged 60.4 $\pm$ 6.6 (Range 40-79) years and when sex was reported (23/26 trials), most randomised participants were male (n = 1522, 76.1%). Preoperative cardiac risk factors were only reported in 10 (34.5%) trials and participants weighed an average of 78.1 $\pm$9.2 kilograms. Type of surgery was reported in 25 (86.2%) trials and coronary artery bypass grafts were the most common procedure performed (n = 1488, 67.8% participants), with 96.6% (n = 2120) of participants having surgery on cardiopulmonary bypass. Postoperative complications were reported in 15 (51.7%) trials with nausea and vomiting listed as a common complication (n = 11, 37.9% trials).

Primary Outcome: Patient Reported Pain Intensity

There was considerable variability in the way measures of patient reported pain intensity were captured (Table 1). Rest pain (n = 26, 89.7% trials) or pain with coughing or movement (n = 4, 13.8% trials) was captured using a 10cm/100mm numerical rating scale (n = 5, 17.2% trials), visual

analogue scale (n = 22, 75.9%), or a non-specified measure (n = 2, 6.9%). Illustrations of instruments or cited sources of instrumentation were rare. Pain was measured every 4 (n = 1, 3.4%), 6 (n = 1, 3.4%), 8 (n = 1, 3.4%), 12 (n = 2, 6.9%), or 24 (n = 10, 34.5%) hours in trials or a mean pain score was provided without a related time point (n = 13, 44.8% trials). A single trial reported proportions of participants with pain at rest at 1 and 3 months (14). Although rest pain was measured in 26 (89.7%) trials there was limited data that could be extracted and used for pooled analyses. A significantly positive intervention effect was reported in 9 (31%) trials. Median scores were provided for 5 (17.2%) trials and mean with standard deviation for 10 (34.5%) trials. Pain at rest in the 10 (34.5%) trials was an average of 3.3 (SD 1.5) in the control and 2.7 (SD 1.9) in the intervention groups respectively. A random effects meta-analysis model of standardised mean differences using the trials that reported average rest pain score at 24 hours illustrated notable heterogeneity (I^2 = 94%, Figure 3) and an effect size that suggested participants in the treatment group were negatively affected by tested interventions (Hedge's g -0.91, 95%CI -1.61, -0.22, p = 0.01). The associated Funnel Plot (Figure 4) illustrated outliers that were removed prior to re-running the analysis to produce a homogenous model with a very similar outcome (Hedge's g -0.66, 95%CI -0.89, -0.43, $p < 0.001$; I^2 = 10%).

Secondary Outcome Measures

No trials compared the effectiveness of multimodal analgesia by contrasting combinations of non-opioid, opioid-agonist-antagonist, partial opioid agonists or full opioid agonists. Most trials (n = 11, 37.9%) compared two different full opioid options for less than 72 hours (n = 24, 82.7%). Nurse initiated (n = 8, 27.6%) analgesic administration or the comparison of full opioid patient-controlled analgesic (PCA) in both groups with placebo, opioid-agonist-antagonist, or partial opioid agonists (n = 11, 37.9%) were common intervention approaches (Table 2). The mean dose of administered analgesic was reported in 17 (58.6%) trials and the ratio of prescribed to administered analgesic for

the first 24-hour intervention interval in these trials ranged from 8.9% to 107% (Table 3). Cumulative 24-hour analgesic requirements and time to first rescue analgesic were not able to be determined. There were no specific intervention related adverse events reported despite protocols enabling between 6 and 936 milligrams of oral Morphine equivalent doses to be administered within 24 hours (Table 3). Length of stay in hospital was reported in 8 (27.6%) trials and did not differ between control (*M* 7.43, SD 1.46 days) and intervention groups (*M* 6.82, SD 2.19 days; t = 0.65(14): *p* = 0.52).

DISCUSSION

Multimodal, opioid-sparing, pain management plans are a key recommendation in ERAS-CS specific protocols (Grant et al., 2024). Findings from this systematic review of RCT testing multimodal analgesic interventions revealed a paucity of robust evidence for multimodal approaches for postoperative pain management. No trials compared the efficacy of non-opioid, opioid-agonist-antagonist, partial opioid agonist, or full opioid agonist modalities. There was notable variability in the approach to, and frequency of, patient reported pain measurement as a primary outcome. Most intervention protocols (n = 24, 82.7%) tested non-opioid and full opioid, or two full opioid combinations, for less than 72 hours in duration from the time of surgery or return to the ICU, and few (n = 8, 27.6%) reported significantly different findings in pain score between groups.

Nurses are primarily responsible for the management of standardised routines in models of care such as ERAS-CS yet are reliant upon medical prescribing to access an adequate array of treatment options. There is an extensive body of evidence to guide optimal approaches to anaesthesia with or without regional adjuncts for adult cardiac surgical candidates, yet very little evidence exists to guide best practice post patient transfer from the operating room or ICU. Patient reports indicate that postoperative ERAS pain is a complex, challenging symptom that impacts discharge planning and recovery (Sibbern et al., 2017). Postoperative pain at rest affects almost 30% of patients up to a

year after surgery (Bjørnnes, Rustøen, et al., 2016) and the relationship between chronic pain and poor postoperative pain management is well established (Gjeilo et al., 2014). When affected by pain, average fiscal costs to the patient are up to CAN$207 a month for the first 6 months after surgery (Guertin et al., 2018). The cost of pain for patients' physical, psychological and quality of life are under-investigated.

The persistent absence of robust data validating multimodal analgesic approaches for pain post-cardiac surgery is a significant problem. Intra-operative management continues to evolve at a rapid pace in the context of minimal preoperative patient engagement in contemporary care. While patients undergoing surgery via a median sternotomy are older, and at greater risk secondary to complex co-morbid conditions and later surgical intervention, in-hospital mortality continues to favorably decline (Jones et al., 2022). The postoperative in-patient interval, however, remains relatively static, irrespective of whether ERAS-CS protocols underpin the model of care (Wong et al., 2016). In low to moderate risk patients low dose opioids do not reduce recovery time (Wong et al., 2016), and as the evidence from this review indicates, opioid analgesics continue to be the main stay of pain management and not necessarily at low dose levels. Length of stay is often underpinned by perioperative complications prolonging duration of endotracheal intubation and ICU stay (Zarrizi et al., 2021) rather than the recovery interval between arrival to the step-down and hospital discharge. It is this interval in which patients are expected to ambulate and engage in deep breathing and coughing exercises. Persistent pain hinders both of these activities (Ouellette et al., 2019) and is also a key driver of unplanned readmission (Iribarne et al., 2014).

Barriers to effective pain management after adult cardiac surgery are attributable to patient, provider, and system level nuances. Patients are poorly equipped to manage their pain in hospital where they are often passive recipients of protocolised approaches (Ouellette et al., 2019). Immediately post discharge, patients are expected to liaise with their primary care provider within a

week, and surgeon or cardiologist within 6 to 8 weeks, but the challenges of securing an appointment time, and the logistics of clinic attendance in this period of transition mean this recommendation is often far from feasible. Pain related misconceptions persist despite well designed preoperative educational interventions (Watt-Watson et al., 2004) and tailored postoperative self-management interventions (Martorella et al., 2018). Divergent views when comparing health professional and patient assessment of pain contribute to inadequate analgesic administration (Fishman et al., 2013) as does inadequate curriculum content in undergraduate education (Barreveld & Griswold, 2018; Shipton et al., 2018).

The findings of this review must be interpreted with caution given the potential risk of bias in reporting of results, measurement of outcomes and deviations from intended interventions in included trials (Figure 2). Studies were heterogenous with considerable variability in intervention design, implementation, duration, and outcome assessment. This heterogeneity impacts on the ability to draw any robust conclusions regarding the effectiveness of the variety of analgesic regimens reported in the studies in this review. A lack of descriptive data, with several authors choosing to illustrate trends in patient reports of pain rather than provide actual data, is another key limitation. Pain measurement was inconsistent in terms of measurement frequency, duration, and instrumentation. All trials in this review used a unidimensional tool for pain assessment, either a numerical rating scale or visual analogue score. A recent systematic review (Baamer et al., 2022) of unidimensional tools found no single tool had superior measurement properties, substantiating the need for comparative studies to establish validity, reliability, measurement error and the limitations of ignoring multiple dimensions of pain in terms of the impact of pain on functional recovery. Many of these trials (n = 21, 72.4%) preceded the publication of CONSORT Guidelines (Schulz et al., 2010) for reporting. The quality of reporting in later trials was consistent with existing evidence of sub-optimal checklist adherence despite journals endorsing checklist completion prior to publication (Nunan et al., 2022).

There is a growing body of evidence linking poorly managed acute pain to the development of chronic pain, yet the number of eligible publications in each of the three decades captured by this review was low. Only seven trials were reported in the last 10 years, the most recent in 2020 (Javaherforoosh et al.). ERAS-CS guideline (Engelman et al., 2019) recommendations are based on moderate quality evidence from one or more well-designed, well-executed, non-randomised or observational studies. Findings from this review indicate minimal interest in investigating the impact of the ERAS-CS recommendations on acute patient recovery. The absence of high-quality evidence from one or more RCT is concerning in the context of over a third of patients reporting persistent pain at rest up to a year after surgery (Bjørnnes, Parry, et al., 2016; Gjeilo et al., 2014). Overall, interventions lacked effect and reported results are indicative of greater interest in opioid consumption than patient pain at rest or with movement during postoperative recovery.

The inclusion and exclusion criteria applied in this review enabled scrutiny of the postoperative recovery interval. Many excluded studies investigated the effect of regional anaesthesia that was notably most often ceased prior to patients ICU discharge. Limiting inclusion criteria to RCT with outcomes captured in the postoperative interval could potentially negate evidence of effectiveness of other approaches to pain management. The purpose of this limitation, however, was to enable the exploration of that interval between ICU discharge (24 to 48 hours after surgery) and hospital discharge, where nurses are responsible for the provision of prescribed pain relief. It is in this interval that patients can be hampered by uncontrolled pain and are expected to actively engage in preparation for discharge as they regain their independence (Guertin et al., 2018). Continuity of care between clinical settings also impacts on the efficacy of optimal pain management during postoperative recovery (Martorella & McDougall, 2021). Cardiac surgery patients commonly experience transitions of care within acute and sub-acute services as they are moved from the operating theatre or post anaesthetic recovery unit to the ICU, to the step-down or high-dependency

unit, and then to the recovery ward or post-acute care unit, prior to discharge into a primary care context. Communication and consistency in treatment is key to effective ongoing pain management during these transitions, to ensure continuity and nurses are the group of healthcare professionals pivotal in ensuring that communication is operationalised into action.

IMPLICATIONS FOR RESEARCH & PRACTICE

Research using novel designs, such as pragmatic RCT and comparative effectiveness trials can address the gaps identified by this review. Specifically, pragmatic RCT to determine the effectiveness of an intervention in a less controlled environment that reflects the real world of clinical practice (Chalkidou et al., 2012). This can be achieved using inclusion criteria that replicate the patient population receiving care, having expert and/or trained clinicians deliver the control and experimental interventions, selecting and implementing validated and reliable outcome measures, and employing fidelity-based strategies to enhance the likelihood of intervention effectiveness. In addition to pragmatic RCT, comparative effective trials compare the risks and benefits of alternative interventions (Chalkidou et al., 2012). Combining these approaches into a pragmatic RCT comparing the effectiveness of non-opioid, opioid-agonist-antagonist, partial opioid agonist, or full opioid agonist modalities will provide evidence necessary to underpin best practice in acute clinical care.

Appropriate outcome measures need to be tested in multisite RCT. There is an urgent need to examine the effect of multimodal analgesics (non-opioid, opioid-agonist-antagonist, partial opioid agonist, or full opioid agonist modalities) on pain intensity at rest, upon movement, and with activity. In addition, the duration of outcome measurement should be over an extended period, preferably greater than 72 hours post-operatively. It would be prudent to consider an examination of longitudinal outcomes associated with cardiac surgical post operative pain management practices on length of stay, development of persistent chronic pain syndromes, and health related quality of life.

Future RCT should actively engage patients, user representatives, caregivers, and the public in the design and implementation of interventions (Greenhalgh et al., 2019). Cardiovascular surgery is constantly evolving in terms of new procedures, interventions and treatment regimes. It is essential to consider the benefits of engaging patients with lived experiences of cardiac surgery and their care partners in the creation and development of research questions and protocols. Including patients from the inception of a cardiac surgery research project throughout its trajectory was referred to by Phillips and colleagues as an integral voice to consider on research teams (Phillips et al., 2024). Given the lack of reporting of actual pain related data experienced post operatively, and the modes of analgesia provided as indicated by the review, including patient and carer voices in the development of research protocols should echo what are perceived as relevant important outcomes for measurement related to pain, and for treatment of cardiac surgical patients' (Phillips et al., 2024) pain. Patient and public involvement (PPI) adds a real-world perspective to the design of studies allowing researchers to capture nuances that may ordinarily be missed (Greenhalgh et al., 2019). Integrating PPI strategies into the design of RCT has been shown to increase the relevance of interventions to patients, increasing the likelihood that participants will adhere to the intervention. PPI strategies have been shown to be beneficial in improving recruitment and retention rates of research participants, to add new and/or unique perspectives to the interpretation of research data that is reflective of patients' lived experiences, to increasing understanding of research priorities that are important to patients and their families, and to enhancing the dissemination of findings beyond academic audiences (Greenhalgh et al., 2019).

From a clinical perspective, nurses are responsible for the management of patients' pain during their post-operative hospital stay. Thus, they are required to have up-to-date knowledge of the most effective pain management strategies as identified in the literature, and to be able to add to the literature by generating evidence through active engagement in the research process (Clark et al.,

2016). However, limited research appraisal skills, reduced funding and protected research time, and poor research infrastructure serve to impede nurses' engagement in the research process, resulting in not all nurses being able to identify or know how to evaluate different pain management strategies. As a result, there is a need for ongoing research training for nurses, the creation of research mentorship opportunities, and increased financial investment in funding nursing research projects. Across cardiovascular settings, this is vital for maintaining and improving care delivery, as having a consistent and valued research culture ensures evidence-based practice is regularly adhered to, while also increasing the likelihood that nurses will seek out innovative, evidence informed approaches for pain management.

In addition to improving clinical nurses' knowledge of pain management, optimising nurses scope of practice with advance practice roles in the clinical context will improve patient outcomes. There is a need for the creation of a cardiac surgery nurse practitioner (NP) or advanced practice nurse (APN) roles that are characterised by specialist post-operative pain management training. This role could provide pain management support during the first year following cardiac surgery. Similar roles exist but are incorporated in a limited number of institutions (Sawatzky et al., 2013). The current post-cardiac surgery NP/APN roles have demonstrated effectiveness in reducing hospital readmission and emergency room rates, while enhancing recovery and patient productivity (Sawatzky et al., 2013).

CONCLUSIONS

This systematic review synthesised evidence of multi-modal analgesic effectiveness for postoperative pain management following ICU discharge, in adults having cardiac surgery. Findings were inconclusive in determining which multimodal analgesic combination was effective in optimising patient recovery after cardiac surgery. Robust, innovative clinical trials designed in collaboration with patient and public involvement in the research process are needed. These will

illicit more meaningful data necessary to determine which multimodal analgesic combination will optimise patient recovery after adult cardiac surgery. In addition, investment in nursing within the cardiac surgery setting is needed to enhance pain assessment and management, along with evidence interpretation, generation, and dissemination for ideal pain treatment. The findings from this review reveal the impact of sub-optimal pain management on postoperative recovery is grossly under-investigated.

Data Availability.

Data will be made available on request.

Conflict of Interest.

No authors have conflicts of interest to declare.

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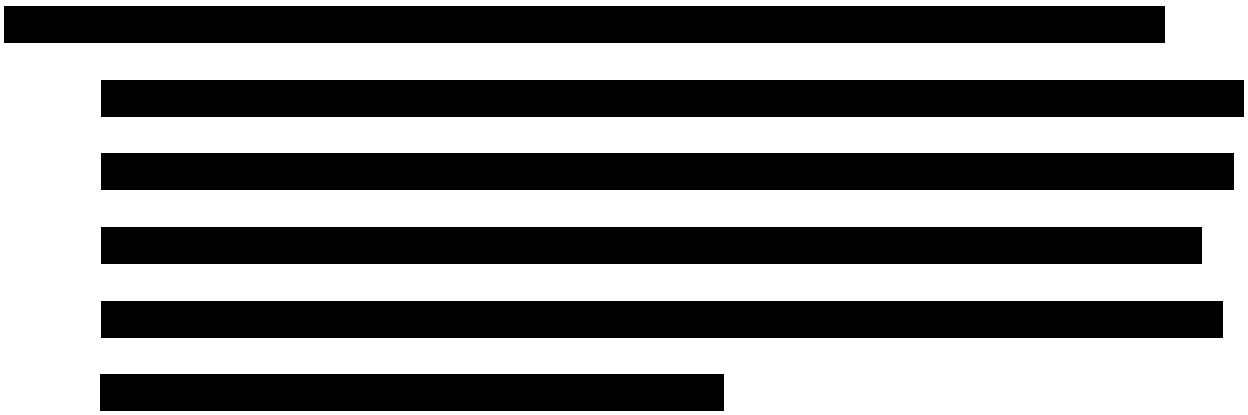

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