MULTIMODAL ANALGESIC EFFECTIVENESS ON ACUTE POSTOPERATIVE PAIN MANAGEMENT AFTER ADULT CARDIAC SURGERY: PROTOCOL FOR A SYSTEMATIC REVIEW.

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Adult #patients report moderate to severe #pain after #CardiacSurgery. What multimodal analgesic combo is best? A Systematic Review #Protocol to find answers @CONNECTcardiac @rochellemwynne @ANZSCTS @GlobalCardiac @CTSCompendium @ctsnetorg @EACTS @CSANZ @heartfoundation @SCTSUK

ABSTRACT

BACKGROUND: Many patients report moderate to severe pain in the acute postoperative period. Enhanced recovery protocols recommend multimodal analgesics but the optimal combination of these is unknown.

PURPOSE: To synthesize the best available evidence about effectiveness of multimodal analgesics on pain after adult cardiac surgery.

METHODS: A systematic review to determine the effect of multimodal postoperative analgesics, is proposed (International Prospective Register of Systematic Reviews Registration CRD42022355834). Multiple databases including the Cochrane Library, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, American Psychological Association, the Education Resources Information Centre the Excerpta Medica database, the Medical Literature Analysis and Retrieval System Online, Scopus, Web of Science and clinical trials databases will be searched. Screening in Covidence® and quality assessment will be conducted by two authors. A grading of recommendations, assessment, development and evaluation summary of findings will be presented if meta-analysis is possible.

BACKGROUND

Generic pain management guidelines do not account for the context of dynamic specialty specific perioperative care. An enhanced recovery after surgery protocol (ERAS) for cardiac surgery (CS) has been developed as a fast-track framework for patient management in this specialist practice domain. Recommendations are based on evidence primarily from single-centre randomized trials that test the effect of interventions in select CS patient cohorts not stratified for age, sex, race, location or other inequities.[1] The ERAS CS protocol is favored as it has significantly reduced time frames for pre and intraoperative care, therefore total length of stay (LOS). The postoperative recovery interval has however, been relatively consistent.[2] The protocol promotes multimodal, opioid-sparing approaches to optimize recovery and prevent chronic pain[3] without specifying recommendations for analgesic administration. Multimodal approaches for analgesia include the administration of a combination of analgesics such as full and partial opioid agonists, opioid agonist-antagonist agents, and non-opioids. Recent trials have revealed multimodal analgesics are associated with reduced LOS,[4,5] cost[6] and postoperative complications[7] in adults after CS but the optimal combination of multimodal analgesic administration is unknown.

Numerous reviews focused on pharmacological interventions for CS pain management reveal equivocal findings.[2] Contemporary trends in practice are indicative of strategies to reduce opioid administration[8] and while the judicious use of opioid analgesics is warranted, it is important to note that low-dose opioid-based anesthesia is not associated with reduced LOS in low to moderate risk CS patients.[2] Furthermore, this approach although widely adopted, is not substantiated with robust evidence[9] and opioid free techniques are not recommended.[10] Notably, findings from nurse-led research indicates over 50% of patients report moderate to severe pain up until postoperative day 4 and a similar proportion of patients do not receive any opioid analgesia.[11] In longitudinal studies almost 30% of patients report persistent postoperative pain at rest up to a year after surgery.[12,13]

Higher analgesic requirements and poorly managed pain in the acute postoperative period, predict the development of chronic pain.[14]

Patients and caregivers, who have the capacity to transform process of care, have been excluded from the development of all but one ERAS protocol, across a range of surgical specialties.[15] This has led to a misalignment in ERAS CS protocol outcome priorities, as outcomes prioritised by patients and caregivers diverge from those of clinicians. Specific to postoperative pain, patients and caregivers prioritize effective, multimodal pain management and a reduction in reliance on pain medications.[16] However, studies underpinning ERAS CS development and those that describe testing the CS protocol in practice, rarely include patient reported postoperative pain score as an outcome measure and although underutilized, opioids continue to be standard treatment for postoperative CS pain.[17,18] The ERAS CS protocol was developed by surgeons, anesthetists, and intensivists. The absence of input from interdisciplinary teams, patients and caregivers in the development phase may underpin the limited effect and unsuccessful implementation of the pain management recommendations in practice to date. To improve pain management after adult cardiac surgery evidence examining multimodal analgesic use is required to determine effectiveness. The purpose of this systematic review is to synthesize the best available evidence about effectiveness of multimodal analgesics on pain after adult cardiac surgery. Integrating existing evidence will reveal the combinations of analgesics used after CS, whether they are in fact multimodal, and which combination has the most effect on patient reported pain.

AIMS

The aim of this systematic review (+/- meta-analysis) is to evaluate the effectiveness of multimodal analgesic administration on patient reported pain and postoperative LOS after adult cardiac surgery. Multimodal analgesia involves any combination of analgesics including full and partial opioid agonists, opioid agonist-antagonist agents, and non-opioids. We hypothesize that

multimodal analgesic administration is superior to non-opioid or isolated opioid analgesics for postoperative pain relief after adult cardiac surgery. Specific review objectives are:

i. To determine type and dose of analgesics used
ii. To determine the ratio of prescribed to administered analgesic
iii. To evaluate the effectiveness of multimodal analgesic administration
    a. On patient reported pain
    b. Postoperative length of stay

METHODS

Design

This review protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols statement[19] and the accompanying elaboration and explanation guide.[20] The methodological approach to this review has been formulated to align with the procedure-specific pain management (PROSPECT) initiative.[21] With the exception of adult cardiac surgery, the PROSPECT group have developed a variety of procedure specific pain management guidelines[22] based on best evidence for analgesic interventions and perioperative pain management for healthcare professionals, enabling the integration of recommendations relevant to practice and procedure specific pathways. Review findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement[23] and the review is registered with the International Prospective Register of Systematic Reviews: CRD42022355834.

Inclusion Criteria

Study selection will be guided by the Population, Intervention, Comparison, Outcome (PICO) mnemonic.[24] We will include studies with adult patients (>18 years) undergoing cardiac surgery (P) that investigated the effect of multimodal postoperative analgesic regimens (I), compared to a control group (C) on patient reported pain (O).

Types of Studies

Primary randomized controlled trials, with a sample size greater than 20 participants in each arm will be included to reduce the risk of outcome bias, as recommended by the International Association for the Study of Pain and the Cochrane Pain, Palliative and Supportive Care Systematic Review Group editors.[25] Systematic reviews, meta-analyses and randomized controlled trials with parallel groups, factorial, cross-over or cluster designs will be included to align with PROSPECT recommendations.[21] Indexed full text papers and abstracts with adequate reporting of intervention and outcomes, published in any language, will be included.

Population

The population of interest is all adult (>18 years) cardiac surgery patients undergoing open heart (median sternotomy) surgery procedures with or without cardiopulmonary bypass involving the heart (coronary artery bypass grafting, valve replacement or repair, repair or replacement of the thoracic aorta involving the aortic valve, neoplasm resection, congenital lesions). If there are multiple procedures included in a study (cardiac in combination with thoracic aortic or thoracic surgery) and data is not reported per procedure type, authors will be contacted to request data tables for specific procedural groups. When studies report pooled patient data involving mixed procedures and data tables are not provided these studies will be excluded.

Intervention

Studies will be included if they test the effect of any multimodal analgesic intervention. Analgesics will be indexed according to potency into groups: full or partial opioid agonists, opioid agonist-antagonist agents, and non-opioids. Analgesics will be reviewed for type of drug, dose available and administered for each postoperative 24-hour intervention interval, route and frequency of administration. Interventions in this review must be administered systemically via enteral (oral, sub-lingual/buccal, rectal), or parenteral routes (transdermal and intravenous, intramuscular, or sub-

cutaneous injection) and effect assessed, in the postoperative period. Studies that include the use of baseline regional anesthesia, and an intervention testing the addition of an enteral or parenteral analgesic, will be eligible for inclusion.

Comparator

Standard care or usual treatment in the comparator group will be described and contrasted with the intervention group. Standard care may involve the administration of full or partial opioids, opioid agonist-antagonist agents, or non-opioids, in isolation or combination, via enteral, parenteral or regional delivery modes.

Outcomes

The primary measure will be patient reported pain intensity at rest and/or during activity (when available) to align with PROSPECT recommendations.[21] The highest patient reported mean pain intensity measurement, captured using validated subjective assessment tools such as the visual analogue or numerical rating scale, will be recorded. These instruments generally measure pain on a 100mm scale or in a format that can be converted to the equivalent and a 10mm improvement or deterioration is associated with a clinically meaningful difference in the context of pain management interventions.[26] Secondary outcomes include the ratio of prescribed to administered analgesic expressed as a proportion, the mean dose of each type of analgesic administered, time to first request for rescue analgesics, cumulative 24-hour analgesic requirements, intervention related adverse events and hospital length of stay in days. Opioid amounts will be converted to oral morphine equivalents as per equianalgesic recommendations.[27]

Exclusion Criteria

We will exclude: (1) non-experimental studies including retrospective or prospective observational cohort, case-control and controlled pre/post intervention studies and studies using registry data; (2) animal studies, and studies of patients having ventricular assist device insertion,

extra-corporeal membrane oxygenation, heart transplantation, minimally invasive surgery, transcatheter interventions and those under 18 years of age; (3) studies testing the effect of regional anaesthesia as an adjunct to multimodal analgesics; (4) studies with an interval that does not include the postoperative recovery trajectory; (5) non peer-reviewed sources (grey literature, web-sites, theses and dissertations); and journals that are not indexed will be excluded.

Information Sources & Search Strategy

The search will not be date restricted to ensure the inclusion of all relevant trials. Databases to be searched include the Cochrane Library, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, American Psychological Association PsycINFO, and the Education Resources Information Centre via the Elton B. Stephens Company platform. The Excerpta Medica database, the Medical Literature Analysis and Retrieval System Online, Scopus and Web of Science will be searched via the OVID platform. PubMed will be searched to capture studies from journals not yet indexed in Medical Literature Analysis and Retrieval System Online. The International Clinical Trials Registry Platform, the Australian and New Zealand Clinical Trials Registry and ClinicalTrials.gov will be searched for unpublished data. Key search concepts are provided in Table 1.

Randomized controlled trials included in primary systematic reviews captured by the search strategy and studies identified by secondary searches of relevant study reference lists will also be eligible for inclusion. Search terms and lists have been developed in collaboration with a senior librarian experienced in the conduct of systematic reviews using MeSH or Emtree terms with appropriate permutations, text words and subject headings, combined with common Boolean operators and symbols for exploding terms (*, +). A preliminary Medical Literature Analysis and Retrieval System Online search to test the search strategy revealed over 700 citations. This search was repeated by the collaborating librarian with replicated results.

Data Management, Selection & Screening

Search results from each database will be imported into Endnote © Version 9.3.3 reference management software and uploaded into Covidence®.[28] Covidence® will be used to facilitate collaborative title, abstract and full text screening, and data extraction. Two reviewers will independently screen the title and abstract of citations with third available to moderate disagreements to reach consensus. Inter-rater reliability assessments will be periodically assessed during the screening process. Eligible articles will be sourced for full-text review that will also involve screening with two reviewers and third available to moderate disagreements to reach consensus. If there are multiple reports of the same study these will be collated so that the study is the unit of interest rather than each report. Exclusion criteria specific to this review will be integrated into the Covidence screening system and captured in screening outcomes illustrated in a Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram.[23]

Data Extraction

The data extraction template in Covidence® will be modified to capture relevant data items. Full text data extraction will be undertaken in duplicate by two reviewers and conflicts resolved with arbitrary discussion. To ensure consistency between reviewers, concurrent periodic meetings will be held during the data extraction process to resolve disagreements by discussion. An additional reviewer will be brought in to adjudicate if there are unresolved discrepancies. Data items for extraction are shown in Table 2. Outcome data extraction will include reported data that may be mean with standard deviation, or median with quartiles, and the number of participants for whom the outcome was measured in each group. Outcome measures will be captured in relation to time intervals (24-hour periods), and effect size-related parameters (frequency, proportion, means, standard deviation, mean difference, 95% Confidence Intervals, probability level).

Quality Appraisal & Risk of Bias

Two reviewers will use the consolidated standards of reporting trials checklist to assess completeness of reporting and methodological quality of included randomized controlled trials. The revised Cochrane Collaboration tool to evaluate trial design, conduct and reporting is built into Covidence® and will be used to risk of bias (RoB V.2.0). As recommended, risks associated with sequence generation, allocation concealment, outcome assessment blinding, incomplete data, selective outcome reporting, and other sources of bias will be categorized as low, high, or unclear. If unclear, an attempt will be made to contact authors for more information. Findings from the risk of bias assessment will be presented in a table to illustrate variability in risk domains for each included study. If the number of included studies is large, then we will also provide a risk of bias graph illustrating the proportion of bias within each domain for all studies. Sensitivity analyses will be conducted to determine the impact of risk of bias on outcomes measures in the context of there being considerable variability in risk of bias.

Data Synthesis

If randomized controlled trials have a parallel group or cluster design treatment arms, time points will be noted to avoid double counting. In crossover randomized controlled trials extracted data will be from the first treatment allocation only. Sample sizes and the number of participants in the treatment or intervention group will be summed. If there is missing data and authors are not responsive, we will follow Cochrane Handbook recommendations to calculate standard deviations from standard errors, confidence intervals or interquartile ranges. Patient reported pain scores will be extracted and the consistency of measurement tools evaluated. Most validated instruments measure pain using either a 100mm visual analogue rating scale or a numerical rating scale with anchors at zero (0) and ten (10), with zero meaning ‘no pain’ and 10 meaning ‘the worst pain imaginable’.[29] The number (n) and proportion (%) of patients prescribed each type of analgesic will be extracted, and the

mean analgesic dose prescribed and administered for each 24-hour postoperative interval. The ratio of prescribed to administered analgesics will be calculated (administered/prescribed x 100/1) and reported as a proportion. Opioid analgesic doses will be converted into opioid milli equivalents to compare mean difference (or standardized mean difference) in opioids prescribed and administered between groups.

If there are comparable trials amenable to meta-analysis, summary estimates will be calculated and effect size will be expressed as weighted (or standardized) mean difference for continuous data, with 95% Confidence Intervals. The distribution of pain scores will be assessed for normality. Meta-analysis will be undertaken using a variation of the inverse-variance method known as the DerSimonian and Laird method for random effects models in RevMan®,[30] as the combination of effect estimates across studies will incorporate an assumption that not all studies are estimating the same intervention effect, rather that estimate intervention effects follow a distribution across studies.[31] Clinical heterogeneity and methodological diversity will be examined by assessing a summary of characteristics of participants and interventions. Sensitivity analyses will be performed to explore the robustness of results according to differences in age, procedure type, potency of analgesia and any additional peculiarities identified. Statistical heterogeneity will be assessed using the chi-squared test with a significance level of $p<0.10$, and the I^2 statistic[32] will be reported to determine the level of variation related to diversity rather than chance.[31] If appropriate, sub-group analyses will be performed to explore differences in patient reported pain according to the timing of intervention initiation (preoperative, intraoperative or postoperative), mode of analgesic administration (parenteral or enteral) and analgesic potency. Funnel plots will be produced using RevMan®[30] and the Egger's test for asymmetry examined if there are concerns regarding non-reporting bias.[33] Pooled results will be graphically displayed in forest plots created in RevMan®.[30]

Meta-Bias

In this protocol specific steps have been articulated to minimize the possibility of meta-bias.[34] Bias in study selection will be reduced by adhering to this protocol that provides a framework for the conduct of the review. The PICO mnemonic refines search terms and ensures the scope of the search is consistent with the aim of the review. The search will be conducted in conjunction with a senior librarian experienced in systematic reviews. We will hand search references lists of systematic reviews not eligible for inclusion to identify potential studies for inclusion and reduce the use of aggregate data. Selection bias will be minimized by using robust citation management software and ensuring there are a minimum of two independent reviewers involved in screening and data collection, with a third for arbitration. To reduce bias associated with the synthesis of studies and promote replicability, this protocol has been prospectively registered. All studies eligible for full text review will have a quality assessment and risk of bias assessment completed independently by two reviewers, with a third available for arbitration. Sensitivity analyses will be undertaken if there is sufficient evidence of low quality or potential sources of bias.

Confidence in Cumulative Evidence

The effectiveness of multimodal analgesic on patient reported postoperative pain will be assessed and reported according to the five grading of recommendations, assessment, development and evaluation criteria; within-study risk of bias, consistency of effect, imprecision, indirectness and publication bias.[31] If data are not suitable for pooled analyses, studies will be grouped for synthesis according to the synthesis without meta-analysis guideline for narrative analysis.[35] The certainty of the evidence for outcomes will be categorized as high, moderate, low or very low.[31]

DISCUSSION

Multimodal, opioid sparing pain control is the central tenant of ERAS protocols. Claims that pain scores are similar between ERAS and traditional care groups, in the context of up to a 70% reduction in oral morphine equivalents, have been validated in a variety of surgical subspecialties,[36]

excluding CS. Consensus recommendations for multimodal opioid sparing perioperative pain management, in ERAS CS protocols, are based on evidence from non-randomized studies. Evaluating the effectiveness of multimodal analgesia in this systematic review will provide evidence to guide procedure specific clinical decision making for postoperative pain management.

Potential limitations of the protocol are related to the exclusion of regional anesthesia as an intervention to achieve analgesia, the inclusion of a variety of CS procedural groups and the requirement for the primary outcome measure to be assessed in the postoperative recovery interval. A key clinical consideration when recommending analgesic interventions is the invasiveness of the administrative technique and risk/benefit ratio.[37] A systematic review of fast-track versus conventional anesthesia after CS excluded studies focused on regional (epidural or intrathecal) blockade as these techniques employ short-acting analgesics[2] and robust meta-analysis indicates minimal benefit from regional anesthesia when compared to conventional anesthesia on postoperative pain and overall recovery.[38] Excluding trials of regional anesthesia improves clinical applicability that underpins our focus on interventions with the greatest relevance for postoperative recovery. In addition, the ERAS CS protocol only refers to the use of analgesics in the postoperative period defined as time from admission to the Intensive Care Unit, or transfer to the recovery or step-down unit, until acute care discharge. If outcomes are reported for aggregate procedures conclusions regarding pain management according to procedure type will be difficult to ascertain. If per procedure outcomes are reported, then sensitivity analyses will be undertaken to examine the effect of procedure type on patient reported pain. Excluding non-randomized studies is an additional limitation as randomized controlled trials may test single analgesic interventions rather than multimodal approaches, but this is also the case in quasi-experimental or observational studies which are more likely to have additional confounding bias'.

Determining the effect of protocol compliance on analgesic use is hampered by variability in ERAS CS implementation at scale. There are significant gaps in clinically relevant research for postoperative pain management after CS, and practice-based change without comparative studies is not unusual. Patient reported pain is one measure of analgesic effectiveness but robust measures of functional status during recovery impacted by pain, such as time to ambulation, are urgently needed in future research. In the interim, this review provides an opportunity to generate evidence to describe analgesic use and multimodal analgesic effectiveness during the acute postoperative recovery of adult cardiac surgery patients. Findings will provide a platform from which procedure specific pain management interventions can be incorporated into refined ERAC CS protocols.

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CRediT

Rochelle Wynne: Conceptualisation, Methodology, Writing – Original Draft, Project Administration; **Suzanne Fredricks**: Conceptualisation, Methodology, Writing – Review & Editing; **Julie Sanders**: Conceptualisation, Methodology, Writing – Review & Editing; **Geraldine Martorella**: Conceptualisation, Methodology, Writing – Review & Editing.

All other authors: Writing – Review & Editing.

What's New?

- Protocols for enhanced recovery after cardiac surgery recommend multimodal analgesics but the optimal effective combination of analgesics is unknown.
- Evidence from this review will inform clinical decision making for postoperative pain management specific to adult cardiac surgery.

Table 1. Search Concepts

Concept 1	**Concept 2**	**Concept 3**
"Cardiac surger*"	"Postoperative"	"Pain management" (by pharmacological agents) OR "pain management outcomes" OR "primary or secondary pain assessment tools"
"Cardiac Surgical Procedures" OR "Thoracic surger*" OR "Heart Surger*" OR "Cardiothoracic surger*" OR "Post-cardiac surger*" OR "Coronary artery bypass graft*" OR "CABG" OR "Cardiovascular surger*" OR "Cardiovascular Surgical Procedure*" or "Cardiac Surgical Procedure*" or "cardio$ surgical procedur$" or "cardiac$ surgical procedur$" or "surgical repair$" or "surgical replacement$" OR "heart-valve-prothesis-implant$" or "myocardial-revascula?ation$" or pericardiostom$ or Pericardiectom$ or Pericardiocentes$ or "aortic-dissection" or "Heart Surger*" or "Cardiothoracic surger*" or "Cardiovascular surger*"	Postoperative OR postoperat$ OR "After cardiac surger*" OR "Postoperat* cardiac" OR "After Cardiac surger*" OR "Postoperative Period" OR "Postoperative" OR "postoperative" OR "post-operative" OR "post-op" OR "postop" OR "after-surger*" OR "postoperative complication" OR "Post-coronary artery bypass graft" OR "Acute postoperat*" OR "Perioperative Period*" or "perioperative care" or "intraoperative care" or "postoperative care" OR perioperat$ or postoperat$ or preoperat$ or intraoperat$	"Pharmacological pain management*" OR "pharmacological pain control*" OR "pharmacological Pain therap*" OR "pharmacological pain treatment*" OR "Pain medicine*" OR "Acute pain management*, pharmacological" OR "pharmacological pain management strateg*" OR "pharmacological pain N2 care" OR "pharmacolog$ pain management strateg*" OR "Pharmaceutical pain management" OR "Analgesic pain management" OR "multimodal analgesic pain management$" OR "non-opioid analgesic pain management" OR "opioid analgesic pain management" OR "Pain management N2 drug*" OR "Pain management W2 drug*" OR "Pain Intensity Score" OR "numerical rating scale" OR NRS OR "pain-intensity assessment" OR "Verbal Rating Scale" OR VRS OR "Faces Pain Scale-Revised" OR FPS-R OR "patients self-report of pain intensity" OR "American Pain Society Patient Outcome Questionnaire" OR "Revised American Pain Society Patient Outcome Questionnaire" OR APS POQ R OR APSPOQ OR "Pain severity assessment*" OR "Intensity of pain assessment*" OR "Pain intensity rating" OR LOS OR "length of hospital stay" OR "Length of stay" OR "quality of life" OR QoL OR morbidity OR "opioid use" OR "Opioid addiction"

Each concept will be combined with "AND"; the * symbol is used to explode key search terms in MEDLINE.

Table 2. Data Items

Study Characteristics	**Patient Characteristics**	**Outcome Measures**
First Author Surname	Age	Pain Score at Rest
Year of Publication	Sex	Pain Score with Activity
Country of Origin	Body Mass Index	Analgesic Types
Study Dates	Comorbid Conditions	Analgesic Doses
Single or Multisite	History of Opioid Tolerance	Analgesic Prescriptions
Study Population	Cardiac Risk Factors	Analgesics Administered
Number of Participants	Surgical Status	Time to Rescue Analgesic
Inclusion Criteria	Anesthestic Technique	Cumulative 24-hour Analgesic doses
Exclusion Criteria	Reoperation	Intervention related Adverse Events
Intervention Evaluated	Cardiopulmonary Bypass	Length of Stay
Treatment in Comparator Group	Operative Category	
Number in Intervention Group	Postoperative Complications	
Number in Control Group		
Duration of Follow-Up		
Number Lost to Follow-Up		
Number Included in Analyses		