BMJ Open

Efficacy of perioperative pain management in paediatric cardiac surgery: a protocol for a network meta-analysis

Haoqi Yan ,[1] Mengxue Yan,[1] Yujun Xiong,[2] Yinan Li,[1] Hongbai Wang,[1] Yuan Jia ,[1] Su Yuan [1]

To cite: Yan H, Yan M, Xiong Y, *et al*. Efficacy of perioperative pain management in paediatric cardiac surgery: a protocol for a network meta-analysis. *BMJ Open* 2024;**14**:e084547. doi:10.1136/bmjopen-2024-084547

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-084547).

HY and MY contributed equally.

Received 22 January 2024
Accepted 27 August 2024

[1]Department of Anesthesiology, Fuwai Hospital, National Center of Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[2]Department of Gastroenterology, Department of Gastroenterology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China

Correspondence to
Dr Su Yuan; fuwaiys@126.com

ABSTRACT

Introduction Congenital heart disease is a common birth defect, but advancements in diagnosis and treatment have improved survival rates. Enhanced recovery after surgery (ERAS) programmes have emerged in paediatric cardiac surgery. Multimodal pain management, as a vital part of ERAS programmes, has been found to be effective in reducing pain and improving outcomes in cardiac surgery patients. Traditional methods of pain control using high-dose opioids can lead to complications, so nonopioid analgesics and regional anaesthesia techniques are being used to reduce the consumption. However, there is a significant variability in pain management practices in paediatric cardiac surgery. A network meta-analysis (NMA) is needed to comprehensively compare the effects of different analgesic interventions in this population.

Methods and analysis A comprehensive electronic literature database search will be performed using electronic databases, mainly including PubMed, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials. All randomised controlled trials associated with perioperative pain management for paediatric cardiac surgery will be included. The primary outcome will be visual analogue score or numeric rating scale of pain and total opioid consumption (or equivalent) 24 hours after postoperative tracheal extubation. The Revised Cochrane Risk of Bias Tool will be employed to assess the quality of included articles. A random-effects pairwise meta-analysis will be performed to report the head-to-head comparison. Following the assessment of individual articles, an NMA will be conducted using a Bayesian framework with random-effects' models.

Ethics and dissemination Ethics approval is not necessary because this study will be based on publications. The results of this study will be published in a peer-reviewed journal.

PROSPERO registration number CRD42023477520.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This research will encompass a comprehensive evaluation of various analgesic interventions, including regional anaesthesia and nonopioid medication in paediatric cardiac surgery.
⇒ The method of network meta-analysis allows for the simultaneous comparison of multiple interventions and can estimate the rank of these therapies, providing further guidance for decision-making in paediatric cardiac surgery.
⇒ We will include only those randomised controlled trials published in English and there are some additional confounders not accounted for in the analysis.

INTRODUCTION

Congenital heart disease (CHD) is the most common congenital malformation diagnosed in newborns.[1] Advances in early diagnosis, cardiac surgery and interventional cardiology have significantly increased CHD survival rates,[2] with the global crude mortality rate declining from 7.1 per 100 000 in 1990 to 2.8 per 100 000 in 2019.[3] Currently, approximately 97% of children born with CHD reached adulthood.[4] Additionally, the wider adoption of minimally invasive surgical techniques has also reduced the length of hospital stays (LOSs) over the past two decades.[5]

Enhanced recovery after surgery (ERAS) programmes have recently been introduced in paediatric cardiac surgery to improve patients' perioperative experience and outcomes.[6] These multidisciplinary programmes aim to reduce surgical stress and enhance recovery through comprehensive perioperative care,[7] including optimising fluid balance and implementing multimodal pain management strategies to minimise opioid use and accelerate recovery.[8]

Multimodal pain management, including perioperative multimodal pain regimen plan and regional anaesthesia, plays a crucial role in ERAS programmes, particularly in cardiac surgery.[9] Effective pain management is essential not only for patient comfort but also for improving outcomes by reducing adverse reactions, such as haemodynamic fluctuation, adverse cardiorespiratory effect and amplification of pain pathways.[10–13]

Traditionally, pain control with high-dose opioids was the primary method in paediatric cardiac surgery.[14] However, these can lead to complications, such as cardiovascular instability and prolonged intubation.[15] According to *The American Association for Thoracic Surgery Congenital Cardiac Surgery Working Group 2021 consensus document on a comprehensive perioperative approach to enhanced recovery after paediatric cardiac surgery,* nonopioid analgesics, including acetaminophen, ketorolac can be an effective opioid-sparing regimen after paediatric cardiac surgery,[6] while peripheral regional anaesthesia and neuraxial anaesthesia have also been proven effective as opioid-sparing methods in paediatric cardiac surgery.[16]

Regional anaesthesia, including local infiltration, peripheral regional anaesthesia and neuraxial anaesthesia, is also a significant part of multimodal analgesia. Research has proven that peripheral regional anaesthesia and neuraxial anaesthesia can be implemented as an effective perioperative opioid-sparing modality in paediatric cardiac surgery.[17] Additionally, due to advances in ultrasound technology, techniques, such as epidural, caudal and peripheral nerve block, are also done safely in the paediatric population with low rates of complications.[18] A meta-analysis conducted in 2019 found that the peripheral regional anaesthesia has been proven to be effective in reducing pain scores, postoperative nausea and vomiting and LOS.[15] On the other hand, neuraxial anaesthesia has also been shown to be effective in reducing postoperative pain. However, there is a low but existing risk of developing epidural hematoma when patients require mandatory anticoagulation for cardiopulmonary bypass.[19] In recent years, a new approach called opioid-free postoperative pain management has emerged specifically for paediatric cardiac surgery patients. Instead of relying solely on opioid pain medications, this approach combines regional anaesthesia techniques and various nonopioid pain medications to manage pain after paediatric cardiac surgeries.[20] Despite the availability of numerous analgesia interventions, the absence of a quantitative and comprehensive evaluation of evidence has led to significant variability in the interpretation and implementation of pain management practices in paediatric cardiac surgery.

Traditional systematic reviews and meta-analyses are useful for comparing the analgesic efficacy between two interventions, but they are limited to direct comparisons from previous trials. With multiple analgesic options available for paediatric cardiac surgery, the traditional method of meta-analysis is insufficient for informed decision-making. On the other hand, network meta-analysis (NMA) offers a more holistic approach to understanding the effectiveness of different therapies. This method allows for the simultaneous comparison of multiple interventions and provides insights into their relative effectiveness. Additionally, an NMA can estimate the rank of these therapies, providing further guidance for decision-making. Given the complexity of pain management in paediatric cardiac surgery patients, it is crucial to conduct an NMA to comprehensively compare the effects of different analgesic interventions.

METHODS AND ANALYSIS

Design

The research will use Bayesian NMA, a statistical method that combines data from multiple studies to evaluate the effectiveness of different interventions. The study protocol has been developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[21] The PRISMA-P checklist of this study is included in online supplemental table 1. Additionally, the protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO), a public database that promotes transparency and reduces the risk of bias in systematic reviews. Any modifications or updates to the study protocol will be promptly recorded and made available through the PROSPERO registration. The study is scheduled to commence on 1 December 2023, and the expected timeframe for completion is 30 June 2024.

Eligibility criteria patients

We will include patients (<12 years of age) undergoing cardiac surgery under general anaesthesia, irrespective of the types and complexity of surgeries. We will exclude studies involving adult patients.

Interventions/comparators

We include all nonopioid pharmacological and non-pharmacological pain interventions currently used in cardiac surgery, nonopioid pharmacological interventions, including but not limited to paracetamol, ketorolac, ketamine, local anaesthetics, dexmedetomidine and gabapentin, while non-pharmacological pain interventions, including regional anaesthesia and local infiltration. The dose and regimen of each pain intervention are not restricted. Considering the possible inconsistency of the innervations, we will analyse pharmacological and non-pharmacological pain interventions separately. We will discuss and resolve any unclear descriptions from the primary studies.

Outcomes

The main outcome(s) will include visual analogue score (VAS) or numeric rating scale (NRS) of pain at postoperative 24-hour total opioid consumption (or equivalent) at postoperative 24 hours.

While additional outcome will include VAS or NRS of pain at postoperative 6–8, 12–16 and 48 hours, total opioid consumption (or equivalent) at postoperative 6–8, 12–16 and 48 hours and opioid-related complications, such as nausea and/or vomiting, pruritus and respiratory depression. Resource utilisation, including the duration of tracheal intubation, LOS in the intensive care unit (ICU) and LOS, can be significantly impacted by various

factors, including the choice of analgesia interventions and their effectiveness in paediatric cardiac surgery.

Study designs

Randomised controlled trials (RCTs) will be included.

Other limitations

Only studies reported in English will be included. Single-arm studies not presenting a comparison will be excluded.

Search strategy

We will perform a systematic search in major electronic databases, such as MEDLINE (PubMed), EMBASE, Web of Science and Cochrane Central Register of Controlled Trials. We will also use other sources, such as hand searching, snowballing of reference lists, conference proceedings and grey literature database. We will search for other relevant trials in the following websites: www.controlled-trials.com/isrctn, www.ClinicalTrials.gov or www.controlled-trials.com.

Additionally, we will contact relevant experts in the field to identify unpublished, ongoing studies or any studies missing from our listed search strategy. The search period will span from the 1960s to November 2023. The keywords include "cardiac surgery", "pediatric", "pain management", "regional anesthesia", "local infiltration", "paracetamol", "ketorolac", "ketamine", "local anaesthetics", "dexmedetomidin", "gabapentin" and other related terms. We will restrict our search to randomised controlled studies. We will publish a complete list of search terms and strategies in the final manuscript. A search strategy (PubMed) is presented in online supplemental table 2.

Data extraction

Data extraction will be performed by two investigators (HY and MY) who will independently screen the titles and abstracts of the retrieved references. We will obtain the full text of potentially included articles and use predefined eligibility criteria to determine inclusion or exclusion. Disagreements will be resolved through consensus deliberation, involving a third investigator (YL) if necessary. The two investigators (HY and MY) will review the included articles and extract relevant data using a standardised form, with a third investigator (YL) conducting a review and resolving any discrepancies. The authors of primary studies will be contacted to obtain any missing information. We will collect the following data: Study characteristics: first author, year of publication, country, type of cardiac surgery and demographics of the patient population. Details of pain modality: pain modality used, timing, route and dosing and any other adjuvant drugs used for study and control groups. Outcomes: pain score at 6–8, 12–16 and 24 hours postsurgery, the total amount of opioid (or equivalent) in the first 6–8, 12–16 and 24 hours postsurgery, the incidence of nausea and vomiting, pruritus, respiratory depression, duration of tracheal intubation, ICU LOS and hospital LOS.

Quality assessment

The methodological quality of RCTs will be thoroughly evaluated by two independent reviewers using the Revised Cochrane Risk of Bias Tool 2.0.34.[22] Various factors contributing to bias will be assessed, including bias derived from the randomisation process, bias due to deviations from planned interventions, bias due to lack of results data, bias in the measurement of the result and bias in the selection of the reported results. Each of these domains will be evaluated for potential risk of bias, which can be categorised into three categories: low risk of bias, some concerns and high risk of bias. These judgements play a crucial role in assessing the methodological quality and validity of the studies conducted within these domains.

Synthesis of included studies

Pairwise meta-analysis

In this study, we will perform a random-effects pairwise meta-analysis to analyse the data. The pooled results will be reported in terms of the mean difference (MD) for continuous outcomes or risk ratio (RR) for dichotomous outcomes. To provide a measure of uncertainty, we will also include the corresponding 95% CIs for the results. To visually represent the results, we will present forest plots. These plots will show the effect size estimates for each individual study, along with their CIs. By examining these plots, we can get a sense of the overall effect size and the variability between studies. To assess the heterogeneity between the included studies, we will use Cochrane's Q-test and the I^2 statistic. Generally, $p>0.1$ and $I^2 \leq 50\%$ are considered to indicate the absence of statistical heterogeneity. In other words, it indicates that the studies are similar enough to be combined and that their results are reasonably consistent with each other. This information will help us determine whether it is appropriate to pool the results from different studies.

Network meta-analysis

Data synthesis

In order to synthesise the included studies, an NMA will be conducted using a Bayesian framework with random-effects models.[23 24] This approach takes into account the underlying variation across studies and allows for a comprehensive analysis. The results for pain score and opioid consumption will be reported in standardised MDs, while dichotomous outcomes will be reported in RRs along with their corresponding 95% CIs. Network plots will be created to visualise the network geometry and assess its feasibility. League plots will present estimated relative effect sizes for all interventions, and interventions will be ranked according to their surface under the cumulative ranking curve (SUCRA) probabilities.[25] A higher SUCRA value indicates a more significant effect in the relevant outcome.

Transitivity analysis

Transitivity analysis will be conducted to determine the validity of indirect comparisons within the network of

treatments. This analysis will involve comparing the characteristics of the population, intervention and study design across the included studies.[26]

Inconsistency analysis

Inconsistency analysis will also be performed to assess the extent of disagreement between the direct and indirect evidence using node splitting analysis.[27 28]

Analysis of subgroups or subsets

If there are high levels of heterogeneity or inconsistency, a sensitivity analysis and/or meta-regression will be conducted to modify the treatment estimates. Additionally, a subgroup analysis will be performed based on the type (eg, open or thoracoscopic) and complexity of surgery (eg, lower complexity congenital heart defects or higher complexity congenital heart defects).

Reporting bias and small study effects

To address reporting bias and small study effects, comparison-adjusted funnel plots and the Egger regression test will be generated for comparisons that involve at least 10 studies. Publication bias will be considered significant if the p value is less than 0.05. All analyses and plots will be generated using Stata V.15.0 and R V.3.4.0, with the appropriate R packages. If quantitative analysis is not feasible, the results will be described narratively.[28]

Quality of evidence

The quality of evidence will be assessed using the grading of recommendations assessment, development and evaluation framework. This approach involves four steps: presenting direct and indirect treatment estimates; rating the quality of direct and indirect effect estimates; and presenting and rating the quality of NMA effect estimates.[29]

Patient and public involvement

Patient or public involvement is not a part of the study design or conduct.

Ethics and dissemination

This research does not require the approval of an ethics committee as it solely relies on reviewing existing literature and does not involve any human or animal subjects. The findings of this review will be published in a peer-reviewed journal.

DISCUSSION

The emergence of ERAS programme in paediatric cardiac surgery has undeniably reduced perioperative stress and accelerated patient recovery.[6] The multimodal algesia management, as a significant part of ERAS programme, has been proven to reduce the LOS, opioid use and postoperative nausea and vomiting (PONV) in patients undergoing cardiac surgery.[30] Generally, the multimodal algesia management includes regional anaesthesia and nonopioid medications. However, despite numerous studies and systematic reviews on individual pain interventions in paediatric cardiac surgery, a universally accepted protocol has yet to be established. Furthermore, conducting extensive RCTs to compare all these interventions would be impractical and costly. Therefore, an NMA will be performed to objectively rank these analgesic techniques.

Several NMAs have been conducted in adult cardiac surgery, including regional anaesthesia and adjuvant nonopioid medication.[31–33] However, no such analysis has been conducted in paediatric cardiac surgery. In paediatric cardiac surgery, previous pairwise meta-analysis has compared the effectiveness of regional analgesia combined with general anaesthesia with general anaesthesia plus systemic analgesia.[15] To our knowledge, there is still a lack of research comparing specific analgesic methods in paediatric surgery.

There are several limitations in this study. First, the different surgical approaches, variations in the nature of cardiac surgery and diverse perioperative care protocols used in the trials led to deviations in the combined results. To address this, we planned to use the surgery time as a proxy for measuring surgical complexity, aiming to mitigate the impact of these variations. Additionally, the diverse reasons for surgery could introduce bias and affect the uniformity of the cohort. The second limitation involves the inconsistency in the types, doses, concentrations and adjuncts used in the various analgesic techniques examined in this NMA. This heterogeneity in the interventions limits the accuracy and reliability of the results. The third limitation is the small sample size in some of the included trials, which increases the risk of sampling errors and undermines the statistical power and generalisability of the findings. Finally, incomplete data in some of the studies included in the analysis could lead to inaccuracies in the results. These incomplete data could stem from missing data points, incomplete reporting or other issues, further affecting the validity of the findings.

Despite the limitations, to our knowledge, this is the first study to compare the analgesic techniques within a single NMA. By providing comparative effectiveness data on various analgesic strategies, the findings will support evidence-based decision-making for pain management in children undergoing cardiac surgery.

Contributors HY, MY and YX are responsible for the conception of the study. HY, MY, YX and YL designed this protocol. HY, YL and HW tested the feasibility of this protocol. HY and MY wrote the original draft. YJ, HW and SY revised the draft. SY is the guarantor.

Funding Supported by the National Clinical Research Center of Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences (Grant No. NCRC2020014) and the National High-Level Hospital Clinical Research Funding (2022-GSP-GG-36)

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Haoqi Yan http://orcid.org/0000-0003-0582-7739
Yuan Jia http://orcid.org/0000-0002-7928-3917
Su Yuan http://orcid.org/0000-0003-3924-7548

REFERENCES

1 Leirgul E, Fomina T, Brodwall K, *et al*. Birth prevalence of congenital heart defects in Norway 1994-2009--a nationwide study. *Am Heart J* 2014;168:956–64.
2 Eriksson G, Liestøl K, Seem E, *et al*. Achievements in congenital heart defect surgery: a prospective, 40-year study of 7038 patients. *Circulation* 2015;131:337–46.
3 Roth GA, Mensah GA, Johnson CO, *et al*. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020;76:2982–3021.
4 Dellborg M, Giang KW, Eriksson P, *et al*. Adults With Congenital Heart Disease: trends in Event-Free Survival Past Middle Age. *Circulation* 2023;147:930–8.
5 Langer NB, Argenziano M. Minimally Invasive Cardiovascular Surgery: incisions and Approaches. *Methodist Debakey Cardiovasc J* 2016;12:4–9.
6 Fuller S, Kumar SR, Roy N, *et al*. The American Association for Thoracic Surgery Congenital Cardiac Surgery Working Group 2021 consensus document on a comprehensive perioperative approach to enhanced recovery after pediatric cardiac surgery. *J Thorac Cardiovasc Surg* 2021;162:931–54.
7 Varadhan KK, Lobo DN, Ljungqvist O. Enhanced recovery after surgery: the future of improving surgical care. *Crit Care Clin* 2010;26:527–47, .
8 Roy N, Parra MF, Brown ML, *et al*. Initial experience introducing an enhanced recovery program in congenital cardiac surgery. *J Thorac Cardiovasc Surg* 2020;160:1313–21.
9 Li M, Zhang J, Gan TJ, *et al*. Enhanced recovery after surgery pathway for patients undergoing cardiac surgery: a randomized clinical trial. *Eur J Cardiothorac Surg* 2018;54:491–7.
10 Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med* 1987;317:1321–9.
11 Pollak U, Serraf A. Pediatric Cardiac Surgery and Pain Management: after 40 Years in the Desert, Have We Reached the Promised Land? *World J Pediatr Congenit Heart Surg* 2018;9:315–25.
12 Wolf AR, Doyle E, Thomas E. Modifying infant stress responses to major surgery: spinal vs extradural vs opioid analgesia. *Pediatr Anesth* 1998;8:305–11.
13 Yamamoto T, Schindler E. Regional anesthesia as part of enhanced recovery strategies in pediatric cardiac surgery. *Curr Opin Anaesthesiol* 2023;36:324–33.
14 Lowenstein E, Hallowell P, Levine FH, *et al*. Cardiovascular response to large doses of intravenous morphine in man. *N Engl J Med* 1969;281:1389–93.
15 Monahan A, Guay J, Hajduk J, *et al*. Regional Analgesia Added to General Anesthesia Compared With General Anesthesia Plus Systemic Analgesia for Cardiac Surgery in Children: a Systematic Review and Meta-analysis of Randomized Clinical Trials. *Anesth Analg* 2019;128:130–6.
16 Suresh S, Long J, Birmingham PK, *et al*. Are caudal blocks for pain control safe in children? an analysis of 18,650 caudal blocks from the Pediatric Regional Anesthesia Network (PRAN) database. *Anesth Analg* 2015;120:151–6.
17 Frankel WC, Maul TM, Chrysostomou C, *et al*. A Minimal Opioid Postoperative Management Protocol in Congenital Cardiac Surgery: safe and Effective. *Semin Thorac Cardiovasc Surg* 2022;34:262–72.
18 Guay J, Suresh S, Kopp S. The use of ultrasound guidance for perioperative neuraxial and peripheral nerve blocks in children. *Cochrane Database Syst Rev* 2016;2:CD011436.
19 Peterson KL, DeCampli WM, Pike NA, *et al*. A report of two hundred twenty cases of regional anesthesia in pediatric cardiac surgery. *Anesth Analg* 2000;90:1014–9.
20 Esfahanian M, Caruso TJ, Lin C, *et al*. Toward Opioid-Free Fast Track for Pediatric Congenital Cardiac Surgery. *J Cardiothorac Vasc Anesth* 2019;33:2362–3.
21 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
22 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
23 Shim SR, Kim S-J, Lee J, *et al*. Network meta-analysis: application and practice using R software. *Epidemiol Health* 2019;41:e2019013.
24 Röver C, Friede T. Using the bayesmeta R package for Bayesian random-effects meta-regression. *Comput Methods Programs Biomed* 2023;229:107303.
25 Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
26 Cipriani A, Higgins JPT, Geddes JR, *et al*. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013;159:130–7.
27 Dias S, Welton NJ, Caldwell DM, *et al*. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932–44.
28 Shim S, Yoon B-H, Shin I-S, *et al*. Network meta-analysis: application and practice using Stata. *Epidemiol Health* 2017;39:e2017047.
29 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
30 Williams JB, McConnell G, Allender JE, *et al*. One-year results from the first US-based enhanced recovery after cardiac surgery (ERAS Cardiac) program. *J Thorac Cardiovasc Surg* 2019;157:1881–8.
31 Hu M, Wang Y, Hao B, *et al*. Evaluation of Different Pain-Control Procedures for Post-cardiac Surgery: a Systematic Review and Network Meta-Analysis. *Surg Innov* 2022;29:269–77.
32 Liu M, Ni R, Huang S, *et al*. Efficacy of non-pharmacological interventions in pain relief and opioid consumption after cardiac surgery: a systematic review and Bayesian network meta-analysis. *J Clin Nurs* 2023;32:4626–37.
33 Zhou K, Li D, Song G. Comparison of regional anesthetic techniques for postoperative analgesia after adult cardiac surgery: bayesian network meta-analysis. *Front Cardiovasc Med* 2023;10:1078756.