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RESEARCH ARTICLE

Determination of the Frequency and Affecting Factors of Chronic Postsurgical Pain After Cardiac Surgery (CPSP-Cardiac): Protocol for a Multicenter, Observational Study

Burhan Dost,[1] Zerrin Sungur,[2] Alper Kararmaz[3] and the CPSP-Cardiac Investigators

[1]Department of Anesthesiology and Reanimation, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye
[2]Department of Anesthesiology and Reanimation, İstanbul University, İstanbul Faculty of Medicine, İstanbul, Türkiye
[3]Department of Anesthesiology and Reanimation, Marmara University Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

This multicenter study aims to investigate the incidence of chronic postsurgical pain (CPSP) after cardiac surgery, exploring the influence of various factors and their implications on patients' quality of life. The CPSP-Cardiac is a large, multicenter, observational study. The target population of 1176 cardiac surgery patients will be recruited from participating hospital sites. Patients undergoing cardiac surgery with median sternotomy for coronary surgery and all open-heart procedures will be eligible for the study. Patients between the ages of 18–80 years who have an American Society of Anesthesiologists Physical Status score of II–III will be included. The primary outcome of our study is to determine the incidence of chronic postsurgical pain in the third month following cardiac surgery, along with identifying the factors that influence it. Our secondary outcomes include assessing opioid consumption in the first 24 hours postoperatively, NRS scores, incidences of postoperative nausea and vomiting, side effects and complications, extubation time, length of stay in the intensive care unit and hospital, chronic pain status at 3 and 6 months, psychological assessments, quality of life, and postoperative complications at 3 and 6 months.

Keywords: Acute pain, cardiac surgery, chronic pain, multicenter study

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Introduction

Cardiovascular diseases represent a widespread global problem affecting a large proportion of the older adult population. Following the increase in life expectancy in recent years, there has been a significant increase in surgical interventions related to cardiovascular diseases.[1] ERAS® Cardiac aims to improve patient outcomes by offering effective perioperative pain control. The goal of pain management is to control acute pain and thereby prevent chronic pain, to provide early mobilization after surgery, to reduce hospital stays, and to increase patient satisfaction and functional recovery.[2] Pain is most intense during the first two days after cardiac surgery and decreases thereafter.[3] Inadequate acute postoperative pain control after cardiac surgery can lead to chronic pain, which affects quality of life.[4] It has been reported that 29% of patients develop chronic postsurgical pain in the first 3 months after cardiac surgery.[5]

Multimodal opioid-sparing analgesia is suitable for cardiac surgery, and a large variety of regional analgesic methods have been studied for efficacy and safety.[2] In recent years, the widespread use of ultrasound in anesthesia practice and the emergence of new regional anesthesia techniques have significantly enhanced acute pain relief. Truncal fascial plane blocks, relatively novel approaches, are increasingly utilized to alleviate postoperative pain and diminish opioid consumption among cardiac surgery patients.[6] The procedure-specific postoperative pain management

Address for correspondence: Burhan Dost, MD. Ondokuz Mayıs Universitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Samsun, Türkiye

Phone: +90 532 704 24 93 **E-mail:** burhandost@hotmail.com

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(PROSPECT) recommends parasternal blocks in cardiac surgery.[7] However, data for the impact of these techniques on chronic pain for cardiac surgery are scant, and further studies are required. This multicenter study aims to investigate the incidence of chronic pain in the 3rd month postoperatively in cardiac surgery and its affecting factors.

Methods

Study Design

This is a multicenter, prospective, observational study. The inclusion and exclusion criteria are based on the literature data on patients who underwent elective on-pump open-heart surgery with median sternotomy. The final version of the participating centers will be attached to the final report of the clinical trial. The protocol follows the principles of "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) and the Declaration of Helsinki (version Fortaleza 2013).

Study Setting and Recruitment

This trial is registered at ClinicalTrials.gov (NCT06382077) and will be conducted as a prospective, multicenter study. Ondokuz Mayıs University Anesthesiology and Reanimation Department will serve as the coordination center. The research team consists of experienced researchers from across the country. The list of study centers, principal investigators, assistant investigators, and other research personnel will be kept as a separate list and will be constantly updated. This list will be included in the final report of the clinical study. The participant's health data confidentiality will be protected by assigning each patient a unique study identification number at inclusion. During and after the trial, all records will be safely stored in password-protected computer files.

Ethics and Dissemination

Chronic Postsurgical Pain-Cardiac (CPSP-Cardiac) has been approved by the Ethics Committee of Ondokuz Mayıs University (2024/130, 13.03.2024). The results will be presented at national as well as international conferences. The final manuscript will be published in a peer-reviewed journal, and results will be used to design further studies.

Participants

The target population of 1176 cardiac surgery patients will be recruited from participating hospital sites. Patients eligible for our study will be undergoing first-time cardiac surgery involving a median sternotomy, including CABG and all open-heart procedures, such as valvular repairs/replacements. Patients between the ages of 18–80 years who have an American Society of Anesthesiologists (ASA) Physical Status score of II–III will be included. Eligible patients will also sign the written informed consent form. Patients will be ineligible if they: (A) are scheduled for minimally invasive cardiac surgery, (B) have BMI>40, (C) have undergone thoracotomy, (D) have alcohol and drug addiction, (E) have severe dysfunction in a significant organ (e.g., presence of severe hepatic or renal disease), (F) have undergone emergency and redo surgeries, (G) cannot be extubated within the first 8 hours postoperatively, (H) have severe psychiatric diseases such as psychosis or dementia that restrict cooperation with the patient (patients who cannot evaluate verbal numerical pain scales), (I) are pregnant or breastfeeding, (J) cannot be reached by phone during the postoperative follow-up periods, (K) cannot communicate in the native language.

Observation

All included patients will be treated according to the standard of care at each participating site. Table 1 outlines this visit schedule.

Primary Outcome

The primary outcome of our study is to determine the incidence of chronic postsurgical pain in the third month following cardiac surgery, along with identifying the contributing factors.

Secondary Outcomes

Our secondary outcomes are to evaluate: (A) Opioid consumption in the first 24 hours postoperatively, (B) Numeric Rating Scale (NRS) scores, (C) The incidences of postoperative nausea and vomiting (PONV), (D) Side effects and complications, (E) Extubation time, (F) Length of stay in the intensive care unit (ICU), (G) Length of hospital stay, (H) Chronic pain status at 3 and 6 months, (I) Psychological assessment, (J) Quality of life assessment, and (K) Postoperative complications at 3 and 6 months.

Observation

1. **Preoperative Questionnaires**

   Following enrollment, standard baseline demographic data including age, sex, height, and weight will be collected, along with clinical characteristics. Additionally, an established psychological assessment, the Hospital Anxiety and Depression Scale (HADS), will be administered to evaluate emotional distress. The HADS comprises seven items each for anxiety and depression, with higher scores on both subscales (HADS anxiety [HADS-A] and HADS depression [HADS-D]) indicating elevated levels of anxiety and depression, respectively.[8]

2. **Chronic Postsurgical Pain**

   The development of CPSP will be assessed using a structured interview protocol, defining CPSP as pain that:

(A) emerges after surgery, (B) is distinct from pre-procedural pain (e.g., preoperative leg pain or angina), (C) is not caused by other factors (such as chronic infection or cancer recurrence), and (D) persists for at least three months. Evaluation will be conducted face-to-face whenever possible, otherwise via telephone. Participants affirming all criteria will be classified as having CPSP ("Yes"), otherwise as not ("No"). For those with CPSP, pain intensity and its impact on daily activities will be gauged using the BPI-SF. This tool includes four 11-point NRS scores assessing average, least, and worst pain intensity over the past 24 hours, as well as current pain intensity (0=no pain, 10=pain as bad as imaginable). BPI-SF's interference subscale will also be employed to measure pain's effect on general activity, mood, mobility, work, social relations, sleep, and enjoyment of life (0=no interference, 10=completely interferes), with a total score derived by summing these items.[9] Dicle et al.[10] conducted a Turkish validity and reliability study of this scale. Supplementary items for pain treatment and body diagram will be utilized for descriptive purposes.

The Leeds Assessment of Neuropathic Signs and Symptoms Pain Questionnaire (S-LANSS) will be used to investigate whether chronic pain is compatible with a neuropathic phenotype, using a cutoff of 12 or greater.[11,12] The Pain Self-Efficacy Questionnaire will be utilized to assess the influence of chronic pain on the individual's daily life. This questionnaire consists of 10 items focusing on the confidence and belief individuals with chronic pain have in carrying out everyday tasks such as household chores, social interactions, and work responsibilities. A cutoff score of 40 or lower suggests low self-efficacy.[13,14]

Complications observed in the first 3 months after admission to the intensive care unit will be recorded. The severity of complications will be evaluated using the 'Clavien-Dindo' classification. Additionally, the 'Comprehensive Complication Index' (https://www.cci-calculator.com/cciCalculator) will be used to evaluate the patient's overall postoperative morbidity.

3. Acute Pain

The NRS score definition will be explained to the patients preoperatively. Regarding the NRS, a 10-cm long chart with the phrases "no pain" on one end and "most severe pain imaginable" on the other will be shown to the patients.[15] They will be asked to assess the severity of their

Table 1. Visit schedule

Assessment	T1 Screening (Premedication visit)	T1 Baseline	T2 Intraoperative	T3 Postoperative 24th hour	T4 Discharge	T5 Postoperative 3rd month	T6 Postoperative 6th month
Informed consent and verification of inclusion criteria	X						
Demographic data		X					
Data related to surgical procedure			X				
Acute pain scores (NRS)				X			
Postoperative nausea and vomiting				X			
Extubation time				X			
Total amount of opioid consumption in the first 24 hours postoperatively				X			
Postoperative complications and side effects				X			
Mortality				X	X	X	X
Lenght of stay, ICU					X		
Lenght of Stay Hospital					X		
Hospital anxiety and depression scale		X				X	X
Brief pain inventory scale						X	X
S-LANSS scale						X	X
Pain self-efficacy questionnaire scale						X	X
Complications						X	X

NRS: Numeric rating scale; ICU: Intensive care unit; S-LANSS: Leeds assessment of neuropathic signs and symptoms pain questionnaire.

pain using this scale. NRS scores will be evaluated in two different ways: at rest and during activity (coughing and deep breathing) after extubation (0), and at 3, 6, 12, and 24 hours postoperatively. Postoperative nausea and vomiting after extubation with the verbal descriptive vomiting score (0=none, 1=mild nausea, 2=moderate nausea, 3=vomiting once, and 4=vomiting more than once) will be evaluated at hours (0), 3, 6, 12, and 24. Also, extubation time (defined as the time until extubation after the patient is admitted to the intensive care unit), total amount of opioid consumption (all opioids used in the first 24 hours postoperatively will be converted to intravenous morphine using the GlobalRPh morphine equivalent calculator (http://www.globalrph.com/narcotic) and a 25% cross-tolerance modifier will be taken into account during this calculation) in the first 24 hours postoperatively, the number of patients requiring rescue analgesia and medications used, and postoperative complications and side effects will be recorded.

Data Collection

This is an observational study where all patients will be treated according to the center's standards. Clinical variables will be obtained from medical records, and demographic and perioperative data, tests used in the study, as well as the important clinical variables will be recorded. Data collection will be conducted pseudonymously, and the patient's name will not appear on any case report forms or clinical study documents. If a patient meets all inclusion criteria and has no exclusion criteria ("eligible"), the patient will be declared included in the study, and patients not included will be informed of the reason for exclusion. Source data include original records and certified copies of clinical findings, observations, or other activities containing all information necessary for the reconstruction and evaluation of this study, in accordance with the ICH E6 Guideline. These source data are documented in various source documents (e.g., hospital records, physician reports, checklists, laboratory reports) and then entered into the e-CRF (Electronic Case Report Form).

Data Records / e-CRF

In this study, a multicenter e-CRF application will be used for data collection. The application will be web-based and will provide services over the internet, with each center being provided access to its own database. The e-CRF application will be developed specifically by the IT vendor and will be integrated into a digital platform sponsored by the Society of Cardiothoracic and Vascular Anesthesia and Intensive Care. The mentioned e-CRFs will be filled out by researchers participating in the study. All e-CRF fields will be checked by the designated working team to ensure proper and complete filling. To assume responsibility for the data recorded, e-CRFs will be individually signed and dated. Patient identifiable information will not be available for data analysis. Data transmission and storage of web-based information are encrypted and will be stored and backed up under the supervision of the Society of Cardiothoracic and Vascular Anesthesia and Intensive Care.

Sample Size

Considering that the prevalence of pain in the opioid group alone is 28%,[5] it is assumed that regional techniques could provide approximately a 30% reduction in chronic postsurgical pain prevalence. Thus, the chronic postsurgical pain prevalence in this group was assumed to be 20%, and the effect size (OR=0.684) was calculated accordingly. With an assumed power of 80%, a Type I error rate of 5%, an Odds Ratio (OR) of 0.684, and an R^2 value of 0.40 for the effects of other independent variables, the required sample size for multiple logistic regression analysis was calculated as 1176. It was planned to recruit at least 1176 patients within a one-year period for our study. In case the sufficient number of patients cannot be reached, the data collection period will be extended to ensure the attainment of an adequate sample size. Power analysis was conducted using G*Power (version 3.1.9.6).

Statistical Analysis

Qualitative data will be summarized with numbers and percentages, and quantitative data will be summarized with mean and standard deviation statistics. Group comparisons for qualitative variables will be made with the chi-square test, and for quantitative variables, the significance of the difference between group means will be assessed with the Welch t-test and analysis of variance. Multiple logistic regression analysis will be performed for the primary outcome variable. In all statistical analyses, interpretations will be made at a 5% significance level.

Conclusion

The CPSP-Cardiac is a large, multicenter, observational study aiming to investigate the incidence of chronic pain in the 3rd month postoperatively in cardiac surgery and its affecting factors. Despite the advancements in cardiac surgical techniques, factors affecting chronic postsurgical pain following cardiac procedures — including the impact of regional techniques — remain inadequately explored. The physiological responses to pain and stress during cardiac surgery, characterized by heightened endogenous catecholamines and potential cardiovascular complications such as tachycardia and hypertension, underscore the critical need for a comprehensive investigation into the management of postoperative pain.[16]

Therefore, our study aims to provide a comprehensive evaluation encompassing acute pain parameters such as pain scores, total morphine consumption, incidence of

nausea/vomiting, and associated side effects, alongside an in-depth analysis of chronic pain characteristics, including its prevalence, intensity, nature, and impact on patients' quality of life. By examining both acute and chronic pain outcomes, our research aims not only to quantify the incidence of chronic pain but also to elucidate the underlying factors contributing to its development and the subsequent implications for patients' well-being and functional status.

Disclosures

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References

1. Laslett LJ, Alagona P Jr, Clark BA 3rd, Drozda JP Jr, Saldivar F, Wilson SR, et al. The worldwide environment of cardiovascular disease: Prevalence, diagnosis, therapy, and policy issues: A report from the American College of Cardiology. J Am Coll Cardiol 2012;60(25 Suppl):S1–49.
2. Wick EC, Grant MC, Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: A review. JAMA Surg 2017;152:691–7.
3. Zubrzycki M, Liebold A, Skrabal C, Reinelt H, Ziegler M, Perdas E, et al. Assessment and pathophysiology of pain in cardiac surgery. J Pain Res 2018;11:1599–611.
4. Mittnacht AJC, Shariat A, Weiner MM, Malhotra A, Miller MA, Mahajan A, et al. Regional techniques for cardiac and cardiac-related procedures. J Cardiothorac Vasc Anesth 2019;33:532–46.
5. Xiao MZX, Khan JS, Dana E, Rao V, Djaiani G, Richebé P, et al. Prevalence and risk factors for chronic postsurgical pain after cardiac surgery: A single-center prospective cohort study. Anesthesiology 2023;139:309–20.
6. Dost B, De Cassai A, Balzani E, Tulgar S, Ahiskalioglu A. Effects of ultrasound-guided regional anesthesia in cardiac surgery: A systematic review and network meta-analysis. BMC Anesthesiol 2022;22:409.
7. Maeßen T, Korir N, Van de Velde M, Kennes J, Pogatzki-Zahn E, Joshi GP, et al. Pain management after cardiac surgery via median sternotomy: A systematic review with procedure-specific postoperative pain management (PROSPECT) recommendations. Eur J Anaesthesiol 2023;40:758–68.
8. Snaith RP. The hospital anxiety and depression scale. Health Qual Life Outcomes 2003;1:29.
9. Cleeland C. The brief pain inventory user guide. Houston, Texas: M.D Anderson Cancer Centre; 2009.
10. Dicle A, Karayurt O, Dirimese E. Validation of the Turkish version of the Brief Pain Inventory in surgery patients. Pain Manag Nurs 2009;10:107–13.e2.

11. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: Validation for use in clinical and postal research. J Pain 2005;6:149–58.
12. Koc R, Erdemoglu AK. Validity and reliability of the Turkish Self-administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire. Pain Med 2010;11:1107–14.
13. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. Eur J Pain 2007;11:153–63.
14. Doğan O, Başkurt F. Pain self efficacy questionnaire anketi`nin (Ağrı öz yeterlilik anketi) Türkçe`ye uyarlanması, geçerliliği ve güvenilirliği. Yüksek Lisans Tezi. Isparta: Süleyman Demirel Üniversitesi, Sağlık Bilimleri Enstitüsü; 2019. [In Turkish]
15. Dost B, Kaya C, Turunc E, Dokmeci H, Yucel SM, Karakaya D. Erector spinae plane block versus its combination with superficial parasternal intercostal plane block for postoperative pain after cardiac surgery: A prospective, randomized, double-blind study. BMC Anesthesiol 2022;22:295.
16. Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000;85:109–17.