Thoracic Paravertebral Adjunctive Dexamethasone Palmitate Reducing chronic pain After cardiac surgery（PANDORA）

Statistical Analysis Plan

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Principle Investigator:

Dr. Chong LEI

Department of Anesthesiology and Perioperative Medicine, Xijing Hospital, Fourth Military Medical University, Xi'an, 710032, China.

E-mail: crystalleichong@126.com

Coordination of the study and data management:

Anesthesia Clinical Research Center (ACRC), Xijing Hospital

Statisticians:

Ms. Manli Huang

Department of Anesthesiology and Perioperative Medicine, Xijing Hospital, Fourth Military Medical University, Xi'an, 710032, China.

Anesthesia Clinical Research Center, Xijing Hospital, Fourth Military Medical University, Xi'an, 710032, China.

DSMB:

Chair: Prof. Huang NIE

Members: Dr. Chunhu GU, Yanyan JIA, Chen LI

Independent Statistician: Chen LI

Version History

Date (dd-mm-yyyy)	Version	Reason for the update
03-16-2024	2.0	Updated Version Number; Updated Secondary Outcome Measures: 1. Morphine consumption Total consumption of rescue analgesia by oral morphine equivalent (mcg/kg) [Time Frame: 24, 48, 72 hours after surgery] 2. The incidence of acute pain at resting and activity Numerical Rating Scale to evaluate the incidence of pain (NRS score range, 0-10; ⩾1 indicates it happens once) [Time Frame: 24, 48, 72 hours after surgery] 3. The incidence of chronic postoperative pain Pain status score on the Brief Pain Inventory (BPI-NRS) score range, 0-10; ⩾1 indicates it happens# [Time Frame: 6 and 12 months after surgery] 4. Pain severity in the past 7 days Patient-Reported Outcomes Measurement Information System (PROMIS) Scale v2.0 - Pain Intensity 3a (T-score range, 36.3-81.8; 81.8 indicates worst pain intensity) [Time Frame: 3, 6, 12 months after surgery] 5. Pain severity in the past 24 hours

		Brief Pain Inventory (BPI pain intensity score rang, 0-40; 40 indicates worst pain intensity) [Time Frame: 3, 6, 12 months after surgery] 6. The interference of chronic postoperative pain on activities of daily living in the past 7 days PROMIS Short Form v1.1 - Pain Interference 8a (PROMIS-PI-SF-8A; T-score range, 40.7-77; 77 indicates worst pain interference) [Time Frame: 3, 6, 12 months after surgery] 7. The interference of chronic postoperative pain on activities of daily living in the past 24 hours Brief Pain Inventory (BPI pain interference score rang 0-70; 70 indicates worst pain interference) [Time Frame: 3, 6, 12 months after surgery] 8. The impact of chronic postoperative pain on neuropathic pain PROMIS Scale v2.0 – Neuropathic Pain Quality 5a (T-score range, 37.0-74.1; 74.1 indicates highly neuropathic pain) [Time Frame: 3, 6, 12 months after surgery] 9. The impact of chronic postoperative pain on health related quality of life 12-item Short-Form Health Survey v2 (SF-12 v2.0 scores range, 0-100, 100 indicates best functioning) [Time Frame: 3, 6, 12 months after surgery]

		10. The impact of chronic postoperative pain on sleep quality Pittsburgh Sleep Quality Index (PSQI score range, 0-21, 21 indicates worst sleep quality) [Time Frame: 3, 6, 12 months after surgery] 11. The impact of chronic postoperative pain on emotional wellbeing Hospital Anxiety and Depression Scale (HADS score range, 0-21, 21 indicates worst anxiety or depression) [Time Frame: 3, 6, 12 months after surgery] 12. The impact of chronic postoperative pain on self-efficacy Pain Self Efficacy Questionnaire (PSEQ score range, 0-60, 60 indicates strongest self-belief) [Time Frame: 3, 6, 12 months after surgery]

BACKGROUND

Approximately one - third of patients undergoing cardiac surgery reported experiencing pain at the 3 - month follow - up, and around 15% reported persistent pain at 1 - year post - surgery [1-3]. The incidence of neuropathic - phenotype pain among these patients was 34%, 39%, and 64% at 3, 6, and 12 months respectively[4]. Chronic postsurgical pain (CPSP) is linked to various complications, such as increased pulmonary and cardiac problems[5] , delayed postoperative ambulation, extended hospital and intensive care unit (ICU) stays, deteriorated recovery and life quality, and elevated short - or long - term mortality[6] . The transition from acute to chronic pain after cardiac surgery is complex and influenced by multiple factors. Surgical tissue damage, along with the subsequent inflammation and nociceptive responses, may be key mechanisms, and the severity of acute postoperative pain [7] is associated with the incidence of CPSP[1] .

Minimally invasive cardiac surgery (MICS) via intercostal incision has been shown to reduce surgical trauma and enhance recovery in cardiac procedures [8, 9]. Nevertheless, patients may still endure significant pain, with some studies reporting no difference[10] or even higher pain levels [11] compared to median sternotomy, particularly when thoracotomy exposure, which may involve rib extraction, muscle division, and intercostal nerve injury [7], is utilized. Consequently, despite implementing a multi - mode analgesia strategy to manage postoperative acute pain[12], the high incidence of CPSP following intercostal - incision minimally invasive surgery remains a major postoperative complication [3].

The Procedure - specific postoperative pain management (PROSPECT) guidelines suggest thoracic paravertebral block (TPVB) as the preferred option for postoperative analgesia after video - assisted thoracoscopic surgery

(VATS) [12]. In thoracic surgery, TPVB effectively alleviates acute pain [13] and improves recovery quality at 24 and 48 hours post - surgery[14]. However, it does not significantly reduce the incidence of CPSP at 3 or 6 months[13]. In breast surgery, TPVB has not proven effective in preventing CPSP at 3 months[15, 16], although it may prevent the transition from acute pain to the neuropathic phenotype of CPSP[16].

The concurrent perineural administration of dexamethasone sodium phosphate (DSP), a well - known local anesthetic adjunct, extends the duration of sensory and analgesic blockade [17, 18], mitigates the cytotoxic effect of bupivacaine, lowers pain scores at rest and during movement, and reduces cumulative morphine consumption at 24 hours [19]. These analgesic advantages of DSP have spurred investigations into its potential for reducing the risk of CPSP. However, in thoracic surgery, combining perineural DSP with ropivacaine for TPVB improves postoperative analgesia quality and shortens recovery time [20], yet does not decrease chronic pain[21]. In the Perioperative Administration of Dexamethasone and Infection (PADDI) trial, an 8 - mg dexamethasone infusion decreased acute pain in non - cardiac surgery but increased the incidence of CPSP 6 months after surgery[22]. Secondary analyses of the ENIGMA - II trial [23] indicated that intraoperative DSP was not associated with the incidence of CPSP in major non - cardiac surgery [24]. Perineural DSP has a ceiling effect on the mean analgesia duration at a 4 - mg dose [25], a short half - life (36 - 72 hours [26, 27]), and may increase postoperative blood glucose concentration [28]. These pharmacological properties may be related to delayed wound healing, increased infection risk, or prolonged mechanical ventilation [29], potentially explaining the controversial impact of DSP on CPSP.

Dexamethasone palmitate emulsion (D - PAL emulsion) encapsulates dexamethasone palmitate (D - PAL) within lipid microspheres to form highly -

loaded, stable, and stealth nanoparticles (DXP - NPs). Compared to free dexamethasone, DXP - NPs exhibit an 8 - fold higher uptake rate and 5 - 6 times greater anti - inflammatory activity, while reducing systemic side effects [30-32]. The long - lasting effect of DXP - NPs has been confirmed in multiple disorders, including macrophage activation syndrome, rheumatoid arthritis, systemic lupus erythematosus, ARDS, and dermatomyositis, with limited adverse effects when administered intravenously or intra - articularly [31, 33-36]. Epidural injection of D - PAL provided enhanced analgesia following intradiscal electrothermal treatment [37].

Consequently, we designed the Paravertebral Adjunctive Dexamethasone Palmitate Reducing chronic pain After cardiac surgery (PANDORA) trial. The trial aims to test the hypothesis that, in adult patients undergoing intercostal minimally invasive cardiac surgery, a single - bolus perineural administration of D - PAL emulsion, as an adjuvant to standard TPVB with ropivacaine, reduces the incidence of CPSP compared to perineural administration of DSP.

STUDY OVERVIEW

Ethics and study design

This single centre, randomized trial is designed to assess the superiority of Thoracic paravertebral block (TPVB) with ropivacaine plus D-PAL emulsion over TPVB with ropivacaine plus DSP on 3-month postoperative chronic pain, among participants planning to undergo intercostal minimally invasive cardiac surgery. The study protocol was approved by the institutional review board

(IRB) at Xijing Hospital (KY20232194-C-1) and has been registered on ClinicalTrials.gov as PANDORA trial with the identifier NCT05920967.

The informed consent will be collected by investigators for all patients before recruitment. Patients have the right to decline consent or withdraw from the trial at any time, and all relevant information related to them will be removed accordingly. The trial protocol adheres strictly to the Declaration of Helsinki, International Conference on Harmonisation - Good Clinical Practice (ICH - GCP), and regulations of the China National Drug Administration (NMPA). The trial protocol has been published on BMJ open on January, 15, 2025 [38].

The intervention drugs will be administered by experienced anesthesiologists and nurses. Adverse events will be continuously monitored and recorded over the 12 - month follow - up period. Any incidences will be promptly reported to the Institutional Review Boards (IRBs) for appropriate action. In the event of serious, life - threatening adverse events (AEs) that result in prolonged hospital stays or death, the trial will be terminated immediately.

Study population

This study is designed to enroll patients within the age range of 18 to 65 years, who have been categorized as NYHA I - III and are scheduled to undergo intercostal incision cardiac surgery. However, several exclusion criteria will be implemented.

Firstly, patients undergoing emergent surgical interventions will be excluded. Emergent surgeries are those that demand immediate attention to address

acute, life - threatening conditions or to prevent significant morbidity.

Secondly, individuals with a Body Mass Index (BMI) of 35 kg/m²or higher will not be included. Obesity, as defined by this BMI threshold, can potentially influence surgical outcomes and is thus a relevant exclusion factor. Thirdly, patients having a documented history of previous cardiac surgeries will be excluded. This encompasses any form of cardiac surgical intervention, regardless of its complexity or nature.

Fourthly, those with a known hypersensitivity to local anesthetics will not be part of the study. Such an allergy can pose substantial risks during the peri - operative period. Fifthly, subjects presenting with skin lesions, trauma, or infectious processes at the site designated for thoracic paravertebral block (TPVB) will be excluded. Maintaining skin integrity at the TPVB site is essential for the safe and effective administration of the block. Sixthly, individuals diagnosed with hepatic, renal, or coagulation disorders will be excluded. These dysfunctions can significantly impact the body's physiological responses during and after surgery, potentially complicating the surgical course.

Randomisation and masking

Eligible participants will be randomised at 1 : 1 ratio via a web-based system (Research Electronic Data Capture; REDCap, developed by Vanderbilt University), where the randomisation seeds are generated by an experienced trial statistician. A permuted block randomisation with random block size 4 or

6 is stratified according to the type of surgery (either with or without cardiopulmonary bypass [CPB]). The blinded allocations will be set up securely to REDCap by the trial statistician and featured with strict encryption for access. This process will be carried out without the involvement of any other individuals.

Group allocation will be concealed from all participants, caregivers, and investigators responsible for outcome assessment and data analysis. Throughout the entire study, only one qualified nurse, responsible for preparing and reconstituting the study drugs, will be unblinded. Given the difference between the lipid emulsion in the infiltration solution and the clear solution, the study drug will be shielded by an opaque cover.

Intervention

Participants will be randomly assigned to receive either 1 ml (containing 4mg) of D - PAL emulsion (manufactured by Guangzhou Green Cross Pharmaceutical Co., LTD, China) or DSP (produced by XinChen Pharmaceutical Co., LTD, China). Each of these will be combined with 20 ml of 0.5% ropivacaine (from RuiYang Pharmaceutical Co., LTD, China). To attain the desired concentration, 10 ml of 1% ropivacaine (RuiYang Pharmaceutical Co., LTD, China) will be diluted with 10 ml of normal saline. Before the surgical procedure, the diluted intervention drugs will be administered as a preemptive bolus for TPVB infiltration using a sterile continuous peripheral nerve block catheter set (B. Braun Melsungen AG). An

18 - gauge needle will be inserted at the designated site, followed by careful placement of a continuous peripheral nerve block catheter within the corresponding paravertebral space. After the surgery, a Patient - Controlled Analgesia (PCA) device will be attached to the catheter. This device will continuously infuse 250ml of 0.2% ropivacaine into the paravertebral space. The background infusion rate will be maintained at 5ml/h, with each PCA dose set at 5ml and a lockout interval of 30 minutes. Given the volume, the PCA will be used for two days post-surgery.

To accurately assess pain intensity, quantitative sensory testing (QST) will be employed to evaluate the degree of pain perception in surgical patients. A single trained investigator, blinded to the group assignment, will conduct the QST using an Electronic von Frey device (EvF device, IITC Life Science, Woodland Hills, CA). The EvF device is equipped with an 800 - g probe having a rigid tip with a diameter of 0.8 mm. The probe is pressed perpendicularly onto the skin surface with a gradually increasing, controlled force. Once the patient senses pain, the result, displayed in grams, is stored, and the probe is withdrawn. Before TPVB, the baseline mechanical pain threshold will be measured by the EvF device at eight markers (T2, T4, T6, T8 along the midclavicular line on both the left and right sides). After the TPVB operation and one day later, the pain intensity will be measured at the same markers to confirm the effectiveness of TPVB. Pain intensity may also be measured on postoperative days 2 and 3 as required.

The PCA regimen will be discontinued when no longer necessary. An electronic memory system will meticulously record each button press, differentiating between valid and invalid presses. For rescue analgesia, if the Numeric Rating Scale (NRS) score exceeds 4 after four PCA boluses, patients will receive intravenous tramadol. The single - dose range is 50 - 100mg, administered via an infusion pump at a rate of 20 - 40mg/h. If tramadol fails to provide satisfactory analgesia, intravenous oxycodone will be administered. A single dose of oxycodone, ranging from 1 - 10 mg, will be given, and subsequent doses will be administered at intervals of no less than 4 hours. The cumulative doses of rescue analgesics will be noted.

Prior to the study's commencement, all investigators will undergo training. All interventions will strictly follow established clinical practice guidelines. During the preoperative visit, eligible patients will be introduced to the pain Numeric Rating Scale (NRS), which ranges from 0 (signifying no pain) to 10 (denoting the most severe pain imaginable). Patients will also receive comprehensive instructions on the proper use of the patient - controlled analgesia (PCA) device.

Data collection and management

Data will be collected at enrollment, end of surgery, ICU discharge, hospital discharge, and 3, 6, and 12 months after surgery. We will document a comprehensive set of baseline characteristics, including demographics,

comorbid conditions, medications, past medical history, and preoperative laboratory test results.

Intraoperative information regarding the dosage, timing, and administration mode of all drugs, along with other surgical details such as cardiopulmonary bypass (CPB) and cross - clamping duration, will be recorded. For the thoracic paravertebral nerve block intervention, data on the operator's proficiency, patients' baseline nociceptive sensations, body positions, block side, administration time, and post-procedure sensation blockade level will also be collected.

Postoperative data documented include medications and fluid balance within the first 24 hours, analgesic drug consumption, and the use of rescue analgesics. Telephone calls will be made by an assigned and trained personnel at 3-month, 6-month, and 12-month, if participants cannot be reached in person. Relevant information such as the incidence, intensity, and phenotype of chronic postsurgical pain (CPSP), quality of life, and any adverse events affecting prognosis will be recorded as reported.

Similar to the randomisation system, data collection and management will also be executed using REDCap 14.0.1 (© 2024 Vanderbilt University). All data will be securely entered and stored within the REDCap application. Identifiable information will be strictly safeguarded, with access limited to the principal investigator (PI). Any access of data shall be request with

appropriate and approved proposal from the PI, and only de-identified data will be provided for research purposes if granted.

Weekly validation will be made by study investigators to ensure quality and integrity, checking for logical consistency and feasibility (e.g., reference ranges, valid values, units). Any identified errors will be traced to their original sources (such as hard - copy case report forms or original electronic system records) and corrected accordingly. Summaries of these corrections will be incorporated into the data quality reports.

STUDY OUTCOMES

Primary endpoint

The primary endpoint is the occurrence of chronic postoperative pain (CPSP) at 3 months after surgery, as defined by the updated International Classification of Diseases (ICD-11). CPSP will be classified as neuropathic pain if it meets the criteria of the Neuropathic Pain Questionnaire (NPQ). In brief, CPSP is characterized by the onset or worsening of pain in the surgical area or its projection to the corresponding nerve-innervated region, persisting for at least 3 months post-surgery. During follow-up, participants will be asked about any ongoing pain or discomfort in the surgical site, thorax (anterior or posterior), axilla, or ipsilateral upper limb. Pain type and intensity will be assessed using the Brief Pain Inventory Short Form (BPI-SF), specifically using the "current" pain situation based on the Numerical Rating Scale (NRS)

score in the BPI-SF (BPI-NRS) to assess whether it occurs. A BPI "current" pain intensity score of ≥1 will indicate the presence of CPSP.

Secondary endpoints

Secondary outcomes will encompass the total morphine equivalent consumption at 24, 48, and 72 hours post - surgery. Also included is the incidence of acute pain at rest and during activity, gauged via the Numerical Rating Scale (NRS) at these time intervals. Chronic postoperative pain will be appraised at 6 and 12 months, with a BPI score above 1 serving as the defining criterion.

Extra assessments will center on patient - reported pain severity in the past 7 days (using PROMIS v2.0 Pain Intensity 3a), postoperative pain intensity in the past 24 hours (BPI), and how chronic pain affects daily activities in the previous 7 days and 24 hours (PROMIS Short Form v1.1 Pain Interference 8a, BPI).

Moreover, evaluations at 3, 6, and 12 months post - surgery will cover neuropathic pain (PROMIS v2.0 Neuropathic Pain Quality 5a), health - related quality of life (SF - 12 v2.0), sleep quality (PSQI), emotional well - being (HADS), and self - efficacy (PSEQ).

Safety and exploratory endpoints

Safety outcomes include the incidence of pneumothorax, hemopneumothorax, hematoma, and associated complications arising after the surgical procedure.

Other safety outcomes are postoperative poor wound healing and adverse reactions such as hyperglycemia, hypoxemia, atelectasis, hypotension, nausea, vomiting, bradycardia, vertigo, agitation, pruritus, chills, and delirium. Outcomes such as the intubation duration, the length of postoperative bed rest, and the hospital stay duration will also be explored, together with stress response markers, measurements of blood glucose, C-reactive protein, white blood cells, and neutrophils will be taken at 24, 48, and 72 hours after surgery. Also, data on the first insulin administration within 24 hours, such as the time, dose, and corresponding blood glucose level, along with the cumulative insulin dose within 48 hours post - operation, will be collected with explored analysis.

STATISTICAL ANALYSIS PLAN

Scope of analysis plan

This plan details the statistical methods for analyzing data from the PANDORA trial to test the hypothesis regarding the superiority of D - PAL emulsion over DSP in reducing CPSP.

Sample size consideration

One-interim analysis was planned at 50% information rate, with both futility and efficacy boundaries. Both alpha and beta spending functions were designed to be based on O'Brien and Fleming methods. To achieve 80% power at 5% significance level, 902 participants are required at 10% drop-out

rate to detect the hypothesized 20% reduction with D-PAL against the 50% CPSP incidence at 3 month.

Datasets for analysis

Analyses will be conducted on an intention-to-treat basis. Patients within the analysing datasets are indicated as in Figure 1 following their randomly assigned treatment arms. Complete-case scenario will be assumed for all outcomes considering the feature of RCT studies; no or at worst very minimal cases shall be missing if there is any. However, should there be any more than 5% missing values observed in outcomes, a sensitivity analysis will be done over the imputed dataset using multiple imputation.

Intention-to-treat (ITT) set analysis considers all randomised patients according to their random allocations. The modified intention-to-treat (m-ITT) population will also be considered to exclude participants who had surgeries canceled after randomisation, or who violated the eligibility after randomization for reasons include but not limited to withdrawn consent.

Analyses for as-treated set will consider the treatment actually received. This takes into account of deviations from the assigned treatment regimen, and considers all cross-overs. Patients for per-protocol population includes only those who completed the full-term intervention as assigned without any major protocol deviations.

Interim analysis and stopping rules

A pre-planned interim analysis at 50% of enrollment will be conducted by the DSMB. Termination will be determined if either of the futility or efficacy bounds based on O'Brien & Flemming functions is met. Precisely, the trial will be effectively stopped when $P < 0.0015$ (i.e., $|z| > 2.963$), and stopped due to futility when $P > 0.2881$ (i.e., $|z| < 0.559$). If the P-value is between these two values, the trial will continue. The trial may also be terminated immediately in case of serious life-threatening AEs leading to prolonged hospital stay or death.

Other termination may occur for individuals on withdrawal of participant consents, temporary or permanent discontinuation of study for patient's best benefits. The patient will still be included in the analysis to uphold the intention-to-treat principle. Data from such patients will be collected until the final follow-up.

Statistical significance and software

Statistical significance is set at 5%. The *rpact* package CRAN R was used for sample size calculation. All statistical analysis will be performed using either R or SAS.

Distribution of subjects

Descriptive statistics will be used to summarize the distribution of subjects across groups in terms of demographic and baseline characteristics.

All randomised subjects will summarise the number of count and percentage of those who completed the study and withdrew early. Reasons of early withdrawals and other termination will also be listed. Summary of subjects with the reasons for non-randomisation.

Protocol deviation

Deviations from the protocol will be documented. Analyses will assess the impact of protocol deviations on the results. List of reasons for deviation shall be provided.

General approach

PANDORA is designed to investigate the superiority of 3-month postoperative chronic pain relief for intercostal minimally invasive cardiac surgery on preoperative use of TPVB with ropivacaine plus D-PAL emulsion relative to TPVB with ropivacaine plus DSP. The test hypothesis assumed a reduction by 20% from 50%. Two-sided hypothesis test at 5% significance level will be considered. Strength of evidence (e.g., confidence intervals or credible sets) will be reported as appropriated together with point estimates. All data will be screened and validated for integrity prior to full analysis.

Baseline and intraoperative characteristics

Baseline information including demographics, preoperative test results will be described using descriptive statistics and presented by treatment groups, as well as intraoperative characteristics. Counts and percentages will be

presented for categorical variables, where percentages are calculated using available data for trial participants. For missing information, the denominator will state as such with no assumptions or imputations made. Continuous variables will be summarised in either mean (±sd) or median (IQR) depending on normality. Alongside p-value < 0.05, baseline variables with standardized differences > 0.131 will also be considered imbalanced. Further adjustment with other statistical concerns will be made for analyses.

Categorical data will be compared using either $\chi 2$ test or Fisher's exact test depending on the incidence rate. T-test or Wilcoxon rank sum test will be used to compare continuous data. Alternatively, non-parametric methods (such as Wilcoxon rank sum test) will be considered where assumptions cannot be made for above tests. Visual assessment of normality will be determined by QQ-plots and residual plots. Transformation of variables such as natural logarithm or square-root transformations will be adapt if needed. We consider 2-tailed 5% statistical tests for main analysis on an intention-to-treat basis for this study.

Blinded Analysis

The primary analysis will be completed using de-identified treatment groups (i.e. treatment A and B). All analyses will be performed and interpreted at this basis until the final unblinding for reporting.

Missing data and outliers

We do not expect any missing primary outcomes considering the natural of

PANDORA studiy designed; if there should be any observed missing primary outcomes, no further imputation methods will be applied for primary analysis. Multiple imputation will be used for missing covariates (<5%) for adjusted analysis and as part of sensitivity analysis for any outcomes missing.

Outliers will be identified as median ± 1.5 IQR (or visuallised using boxplots). They will need to be validated by medical experts before any movement (e.g., correction, removal or replacement) made. Their impact on results will be assessed.

Data presentation

Overall and by-group descriptive statistics will be presented for all baseline, preoperative and intraoperative information. Categorical data will be presented as counts (percentage); detailed whole population, missingness, frequencies or each component level of composite variable will be presented. Continuous data will be presented as mean (± sd) or median (IQR); number of missing values will also be summarised.

Computation of date objects and durations

Dates will be managed using *lubridate* package in R and analysed according to standard methods in the chosen statistical software. Time duration will be calculated based on the relevant time points as described in the study protocol.

Date of discharge from hospital - date of index surgery +1

For non-specified dates, 1st day of the calendar month will be assumed. For

vague dates reported, (e.g., as the first, middle or last third of the month), the day considered will be the 5th, 15th or 25th of the month. For non-reported time, 8.00 am will be assumed.

Primary analysis methods

The primary outcome will be reported as counts and percentages and compared using Chi-squared test. Risk difference and 95% confidence interval will be reported. Risk ratio with a 95% confidence interval will be estimated using Wald's likelihood ratio approximation test. For adjusted analysis, generalised linear models under binomial family will be used and appropriate link functions (either log or logit) will be used. Odds ratios or relative risks together with 95% confidence intervals will be reported; on appropriate estimates for relative risks, methods such as bootstrap, Poisson regression approximations can be applied. Adjustment on stratification variables such as surgical procedure will be made; unadjusted comparisons will use stratified Chi-squared comparisons, and adjusted estimates will be made via generalised linear mixed effect models treating surgical procedure as random intercept. Again, 95% confidence intervals will be reported with point estimates.

Sensitivity analysis methods

Several predefined sensitivity analyses are as followings: 1. the BPI-NRS score will be treated as a continuous numeric variable and compared with t-tests; 2. adjusted analysis will be conducted using appropriate regression methods (e.g.,

linear regression, log-Gaussian regression, etc), where between-group differences will either be provided as standardised mean difference or standardised median difference, with 95% confidence intervals reported; 3. If more than 5% of primary outcome data is missing, multiple imputations will be carried out and imputed set will be used as an analytical set for sensitivity analysis; 4. the same analytical procedure in ITT analysis will also be conducted over per-protocol set; 5. between-group interactions on timing will be tested for BPI-NRS score at 3, 6, and 12 months using repeated measure ANOVA.

Secondary analysis methods

All secondary outcomes will be analysed according to the intention-to-treat principle. Proportion of patients experiencing secondary endpoints including acute pain at rest and during activity, chronic postoperative pain at 6 and 12 months will be reported. The total morphine equivalent consumption at 24-, 48-, and 72-hours post-surgery will be reported as mean (sd) or median (IQR). Similar applies to the patient-reported pain severity in the past 7 days (using PROMIS v2.0 Pain Intensity 3a), postoperative pain intensity in the past 24 hours (BPI), and how chronic pain affects daily activities in the previous 7 days and 24 hours (PROMIS Short Form v1.1 Pain Interference 8a, BPI).

Moreover, evaluations at 3-, 6-, and 12-months post - surgery will cover neuropathic pain (PROMIS v2.0 Neuropathic Pain Quality 5a), health - related quality of life (SF - 12 v2.0), sleep quality (PSQI), emotional well - being (HADS), and self-efficacy (PSEQ).

Similar techniques will be used for secondary analysis; crude comparisons for will use the Chi-squared test, with risk differences and relative risks and their respective 95% confidence intervals provided. For binary data, binomial regressions with log or logit links will be employed. For continuous responses, linear regressions with appropriate transformations will be conducted. For time-to-event data, non-parametric inspection will be done using Kaplan-Meier curves, and hazard ratios with 95% confidence intervals will be estimated using Cox proportional hazard models. Death will further be treated as a competitive event using competing risk models

Safety outcome analysis methods

Incidence of all adverse reactions will be reported with reasons listed. Analysis of these adverse reactions will be compared using Chi-squared or Fisher's exact tests. Judgement of whether the safety outcomes are relevant to the study is determined by the steering committee and compared, with list of reasons will be provided.

Pre-defined subgroup analyses

Pre-planned subgroup analyses will examine factors such as age (based on the cohort median), gender (male, female), BMI (≤ 24, >24), incision type (video-assisted thoracic port incision involving multiple intercostal spaces versus a single long intercostal incision), CPB (yes, no), and block side (left, right). Interaction effects will be evaluated by including interaction terms between the

stratified variables and intervention groups in the relevant models. An exploratory analysis will also investigate the interaction between the randomization group and different time points for repeatedly collected secondary outcomes, with risk ratios and 95% confidence intervals calculated. The duration of intubation, postoperative bed rest time, and length of hospital stay will be analyzed using survival analysis techniques. Stress response markers, data on the first insulin administration within 24 hours, and cumulative insulin doses within 48 hours will be reported and compared without adjustments for multiple comparisons.

Other explorations

The Acceptability Curve Estimation using Probability above Threshold (ACCEPT) analysis will be adapt to see the true difference between treatments exceeding various acceptability thresholds based on the trial data. Limitations of traditional binary trial conclusions will be assessed via ACCEPT in this PANDORA study.

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