Protocol Clinical Trial

Effect of cryoablation of intercostal nerves on pain in the early postoperative period in patients with minimally invasive mitral valve surgery: a pilot prospective randomized study (BLOCK trial).

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Background

Cardiovascular diseases are one of the main causes of death worldwide. According to pathological studies, heart defects occur in 4-7% of cases, and the most common defect among the defects is damage to the mitral valve [1]. Significant advances in surgical practice, instrumentation, tissue manipulation, and perfusion technology have made it possible to perform mitral valve surgery using mini-approaches. Minimally invasive mitral valve surgery has become the standard of care in some specialized cardiac centers around the world due to its excellent results, even despite longer cardiopulmonary bypass times and aortic occlusion. In 2008, P. Modi and co-authors, a meta-analysis has been published in which the authors come to the conclusion that a minimally invasive approach for correcting mitral valve pathology actually has significant advantages: early activation of patients, shorter duration of stay in the recovery room, shorter wound healing times, advantages in case of repeated interventions, less the number of bleedings and purulent-septic complications compared to classical sternotomy [2]. But despite all the advantages of this approach, severe pain after minimally invasive cardiac surgery continues to remain a serious problem [3]. Acute pain occurs after dissection of the chest, pleura and pericardium, compression of the intercostal nerve with a retractor, as well as dissection of the intercostal and pectoral muscles during surgical access. It limits breathing and cough in the postoperative period, which can subsequently lead to hypoxemia, sputum stagnation, atelectasis, pneumonia, myocardial ischemia, slow recovery, and also an increase in the length of hospitalization [4]. Therefore, additional emphasis and attention is paid to protocols for early functional restoration and pain reduction for this group of patients. There are protocols for “enhanced recovery after surgery” (ERAS - Enhanced Recovery After Surgery), their use makes it possible to achieve shorter stays in the intensive care unit, reduce hospitalization, improve treatment outcomes and reduce financial costs. One of the components of ERAS is the use of additional pain management modalities [5]. However, in cardiac surgery, traditional methods of regional anesthesia, such as thoracic epidural anesthesia or paravertebral block, are not usually used due to intraoperative heparinization and the associated higher risk of spinal or epidural hematoma. Finding an optimal and effective pain management strategy for this category of patients remains an unsolved problem today.

Intercostal nerve cryoablation is considered a relatively new treatment for postoperative pain in patients undergoing minimally invasive mitral valve surgery. One of the first studies of cryoneurolysis was conducted back in 1974 in thoracic surgery [9]. In 76 patients, the use of intercostal cryoablation resulted in a significant reduction in postoperative opioid analgesic consumption. These results were subsequently confirmed in several other studies and the data were retrospective. In 2000, a prospective randomized controlled trial was published involving 30 patients who underwent minimally invasive mitral valve surgery or minimally invasive coronary artery bypass grafting and underwent intercostal

cryoablation. According to the results, a decrease in postoperative pain syndrome was observed, and less painkillers were required [10].

In the study O'Connor LA et al. in patients undergoing surgical stabilization of the ribs, cryoablation of the intercostal nerves resulted in a 25% reduction in opioid analgesics consumption compared with patients who received an extrapleural catheter, and pain scores were reduced by 22% in the cryoablation group [7]. Similar results (cryoablation made it possible to significantly reduce morphine consumption compared to the control group and reduce pain) were also described inrecent retrospective studies through 2023 in other patient groups: patients who have undergone pulmonary resectionusing single-port thoracic video-assisted access, where cryoablation was used as a method of postoperative pain relief [8] and patients undergoing lung transplantation [12].

In the FROST study for 2021 the use of this method in patients with lateral thoracotomy showed significant improvement in spirography parameters (FEV1, FVC) after 48 hours, as well as 30 and 60 days after surgery [6]. Studying the influence of pain was not the main objective of this work; pain was assessed using VAS and did not show a difference. However, improvement in breathing parameters in the early postoperative period may indirectly be associated with a lower level of pain and a more comfortable state of the patient; the consumption of opioid analgesics was not properly assessed in this study.

In 2021 Peter I Cha and others published a systematic review of 23 studies on the effectiveness of intercostal cryoneurolysis in patients with pectus excavatum, lateral thoracotomy, post-thoracotomy pain syndrome, traumatic rib fracture and chest wall malignancy. Most studies have demonstrated a reduction in opioid analgesic use with intercostal nerve cryoablation compared with traditional pain management techniques. In patients requiring lateral thoracotomy, intercostal cryoablation results in decreased opioid analgesic dosage (grade 2A) and improved pain scores (grade 2C) postoperatively (PICO guidelines) [11].

Finding an effective and at the same time simple strategy for pain relief in the early postoperative period in patients undergoing minimally invasive mitral valve surgery is an urgent task; it is advisable to conduct a prospective clinical study with a well-thought-out design in this direction.

Study design

A single-center pilot prospective randomized clinical trial is planned, with a 1:1 allocation ratio.

Objectives

To determine whether cryoablation of intercostal nerves provides a clinically significant analgesic effect, which is reflected in a decrease in opioid analgesics consumption and in a decrease in pain according to VAS in patients undergoing minimally invasive mitral valve surgery. To obtain preliminary data for planning a subsequent larger prospective randomized trial.

Research aims:

1. Conduct a comparative analysis of the data on the opioid analgesic consumption necessary for pain relief when using cryoablation of intercostal nerves and the standard treatment protocol in patients with minimally invasive mitral valve surgery.
2. To conduct a comparative assessment of pain syndrome according to VAS in patients in the intercostal nerve cryoablation groups and the standard treatment protocol in patients with minimally invasive mitral valve surgery.
3. Assess spirography parameters (FEV1, FVC) before surgery, 48 hours after surgery and before discharge when using cryoablation of intercostal nerves and the standard treatment protocol in patients with minimally invasive mitral valve surgery.4. To evaluate the incidence of side effects and the need for inotropic and vasopressor support in the early postoperative period in the intercostal nerve cryoablation and standard treatment protocol groups in patients undergoing minimally invasive mitral valve surgery.
5. To evaluate the duration of mechanical ventilation in the postoperative period when using cryoablation of intercostal nerves and the standard treatment protocol in patients with minimally invasive mitral valve surgery.
6. Assess the length of stay in the ICU and the duration of hospitalization when using cryoablation of intercostal nerves and the standard treatment protocol.
7. Assess the presence of chronic post-thoracotomy pain syndrome in the postoperative period after 2 and 6 months and the presence of side effects after cryoablation of intercostal nerves (paresthesia in the area of surgical access and in the right arm).

Research participants

30 patients (15 patients in each group) who are scheduled to undergo minimally invasive mitral valve surgery under cardiopulmonary bypass.

Inclusion criteria

- Written informed consent;

- Minimally invasive mitral valve surgery.

Non-inclusion criteria:

-patient refusal;

- pregnancy;

- treatment with antidepressants or epileptic drugs;

- depression, which can significantly affect the perception of pain;

- chronic use of analgesics;

- participation in competing randomized clinical trials.

Exclusion criteria:

- Extended mechanical ventilation, more than 12 hours.

Randomization, allocation, blinding

A block will be used to distribute participants into groups randomization with block lengths of 2 and 4. Masking will be performed for the statistician. Sample size calculation was not performed because no data were available to estimate sample size.

Description and rationale for the route of administration, dosage, dosage regimen and course of treatment

Patients undergoing minimally invasive mitral valve surgery while on cardiopulmonary bypass will be randomized into two groups:

1. Patients receiving cryoablation of intercostal nerves (CryoINB) as a method of pain relief.
2. Patients who will undergo a standard pain management protocol.

Patients in the CryoINB group will undergo cryoablation of the intercostal nerves, at the end of surgery before weaning from CPB, using the «ArtiCue» device for 120 seconds at a temperature of -50°C to -70°C, in the intercostal spaces where the surgical approach is located, one intercostal space above and one below it. Cold leads to axonotmesis, in which the axon and myelin sheath are damaged, preventing the pain signal from traveling along the sensory nerve. However, the structural elements of the nerve are preserved, which promotes complete regeneration at a rate of 1–2 mm per day, thereby restoring normal function within several months.

Patients in the group with the standard anesthesia protocol will receive an intercostal block in the area of surgical access - a single injection of 0.75% ropivacaine solution 20 ml. A local anesthetic will be injected into the area of the posterior wall of the chest 2 cm lateral to the sympathetic trunk under the parietal pleura in the intercostal space along the intercostal nerve, where the surgical approach is located [14].

All study participants will receive postoperative pain management according to the protocol described below:
If VAS >4 points on the scale, patients will receive NSAIDs (paracetamol 1 g IV) [15, 16]. The maximum daily dose will be 4 g/day.
If there is no effect after 30 minutes, opioid analgesics will be administered (MORPHINE 10 mg). The maximum daily dose of opioids for adults will be 50 mg.
If other opioid analgesics are administered, they will be converted to morphine equivalent (MME) [13].

Drug	Conversion factor to morphine	Conversion factor from morphine	Equianalgesic dose	
			IM/IV (mg)	PO (mg)
Morphine	1	1	10	30
Hydromorphone	×5	1/5	1.5	7.5
Oxycodone	×1.5	1/1.5	–	20
Hydrocodone	×1	×1	–	30
Fentanyl	×100	1/100	–	0.1
Codeine	/10	×10	130	200
Nalbuphine	×1	×1		
Oxymorphone	×3	1/3	1	10
Tapentadol	×1	×1		
Tramadol	/10	×10	100	120
Buprenorphine	×10	1/10	0.3	0.4 (SL)
Meperidine	/10	×10	100	300
Methadone	–[a]	–[a]	1	2

(Dott D., Sobey CM Common Opioids //Hospitalized Chronic Pain Patient: A Multidisciplinary Treatment Guide. – 2022. – P. 151.)

Primary outcome:
The opioid analgesic consumption within 48 hours after surgery, calculated in milligram morphine equivalent (MME).

Secondary endpoints:

- The intensity of pain, assessed using a visual analogue scale (VAS) after extubation,
  6, 12, 24, 36, 48 hours after surgery
- Dynamics of spirography (FEV1, FVC) before surgery, 48 hours after surgery, before the patient's discharge
- Frequency of side effects (nausea, vomiting, etc.)
- Need for inotropic/vasopressor support
- Duration of mechanical ventilation
- Duration of ICU stay
- Duration of hospital stay
- Follow-up after 2 and 6 months (CPPS, numbness in the right arm and in the area of surgical access)

Statistical analysis

Comparisons of continuous outcomes will be made using the Mann-Whitney test for non-normal variables and the Welsh t test for normal variables. Comparisons of binary outcomes will be made by the chi-square test or Fisher's exact test.

Data processing

All information will be collected by staff using paper documentation, the data of which will then be entered into an electronic database.

Initial data

1. Demographic indicators: age, gender, height, weight, body mass index.
2. Disease severity: left ventricular ejection fraction, left ventricular EDV, presence of mitral regurgitation, degree of mitral regurgitation, peak mitral valve gradient, pulmonary artery pressure, FAC (Fractional Area Change), history of cardiac surgery, NYHA class, EuroSCORE II risk.
3. Concomitant diseases: myocardial infarction, arterial hypertension, diabetes mellitus, atrial fibrillation, ventricular extrasystole, COPD, chronic kidney disease, stroke, epilepsy.
4. Taking the following medications: antidepressants, antiepileptic drugs, long-term use of NSAIDs (more than 14 days), opioid analgesics.

During the operation:
1. Type of surgery (mitral valve repair or replacement).
2. Time of heart-lung bypass (minutes).
3. Aortic occlusion time (minutes).
4. Minimum temperature during surgery.
5. Dose of fentanyl per operation (mg/kg).
6. Inotropic index.

Period of hospitalization and stay in the ICU:
1. Dose of opioid analgesics 48 hours after surgery (morphine in MME).
2. Assessment of pain intensity using a visual analogue scale (VAS) after extubation, 6, 12, 24, 36, 48 hours after surgery.
3. Duration of mechanical ventilation (in days).4. The presence of side effects (nausea, vomiting).
5. Need for inotropic and vasopressor support, VIS.
6. Surgery complications (pulmonary edema, bleeding, febrile seizures, heart failure, respiratory failure, myocardial infarction).
7. Duration of stay in the ICU (in days).
8. Duration of hospitalization (in days).
9. The result of spirography before surgery, 48 hours after surgery and before

discharge.

Ethical issues

The study will not be launched until approved by the Ethics Committee. Eligible patients will be included in the study after signing informed consent.

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Registration

After Ethics Committee approval, the study will be registered on ClinicalTrials.gov.

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