Trials

STUDY PROTOCOL

Open Access

Effect of non-steroidal anti-inflammatory drugs on the management of postoperative pain after cardiac surgery: a multicenter, randomized, controlled, double-blind trial (KETOPAIN Study)

Pierre Huette[1*], Mouhamed Moussa[2], Momar Diouf[3], Thomas Lefebvre[1], Guillaume Bayart[1], Mathieu Guilbart[1], Christophe Viart[1], Guillaume Haye[1], Stéphane Bar[1], Thierry Caus[4], Sandrine Soriot-Thomas[5], Sophie Boddaert[6], Hamza Yahia Alshatri[7], Paul Tarpin[1], Ottilie Fumery[1], Christophe Beyls[1,8], Hervé Dupont[1], Yazine Mahjoub[1,8], Emmanuel Besnier[9] and Osama Abou-Arab[1,10]

Abstract

Background Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended for the management of acute postoperative pain as part of a multimodal strategy to reduce opioid use, relieve pain, and reduce chronic pain in non-cardiac surgery. However, significant concerns arise in cardiac surgery due to the potential adverse effects of NSAID including increased bleeding and acute kidney injury (AKI). We hypothesized that NSAIDs are effective against pain and safe in the early postoperative period following cardiac surgery, taking contraindications into account.

Methods The KETOPAIN trial is a prospective, double blind, 1:1 ratio, versus placebo multicentric trial, randomizing 238 patients scheduled for cardiac surgery. Written consent will be obtained for all participants. The inclusion criterion is patients more than 18 years old undergoing for elective cardiac surgery under cardiopulmonary bypass (CPB). Patients will be allocated to the intervention (ketoprofen) group ($n=119$) or the control (placebo) group ($n=119$). In the intervention group, in addition to the standard treatment, patients will receive NSAIDs (ketoprofen) at a dose of 100 mg each 12 h 48 h after. The control group, in addition to the standard treatment, will receive a placebo of NSAIDs every 12 h for 48 h after surgery. An intention-to-treat analysis will be performed. The primary endpoint will be the intensity of acute postoperative pain at rest at 24 h from the end of surgery. Pain will be assessed using the numerous rating scale. The secondary endpoints will be postoperative pain on coughing during chest physiotherapy, postoperative pain until day 7, the pain trajectory between day 3 and day 7, cumulative opioid consumption within 48 h after surgery, nausea and vomiting, the occurrence of postoperative pulmonary complications within the first 7 days after surgery, neuropathic pain at 3 months, and quality of life at 3 months.

Discussion NSAIDs function as non-selective, reversible inhibitors of the cyclooxygenase enzyme and play a role in a multimodal pain management approach. While there are recommendations supporting the use of NSAIDs

*Correspondence:
Pierre Huette
huette.pierre@chu-amiens.fr
Full list of author information is available at the end of the article

in major non-cardiac surgery, recent guidelines do not favor their use in cardiac surgery. However, this is based on low-quality evidence. Major concerns regarding NSAID use in cardiac surgery patients are potential increase in postoperative bleeding or AKI. However, few studies support the possible use of NSAIDs without the risk of bleeding and/or AKI. Also, in a recent French survey, many anesthesiologists reported using NSAIDs in cardiac surgery. To date, no large randomized study has been conducted to evaluate the efficacy of NSAIDs in the management of postoperative pain in cardiac surgery. The expected outcome of this study is an improvement in the management of acute postoperative pain in cardiac surgery with a multimodal strategy including the use of NSAIDs.

Trial registration ClinicalTrials.gov NCT06381063. Registered on April 24, 2024.

Keywords Cardiac surgery, Outcomes, Acute postoperative pain, Non-steroidal anti-inflammatory drugs, Pain intensity, Multimodal pain management

Background

A multimodal pain management strategy, including non-steroidal anti-inflammatory drugs (NSAIDs), has been shown to be effective in major non-cardiac surgery allowing better pain management while reducing opioid consumption and chronic pain [1, 2].

There is growing evidence that multimodal opioid-sparing approaches can adequately address pain through the additive or synergistic effects of different types of analgesics [3, 4]. NDAIDs are non-selective reversible inhibitor of the cyclooxygenase (COX) enzyme and have a place in this multimodal strategy with a significant decrease in pain intensity [5].

Cardiac surgery is a major source of postoperative pain. Studies have reported pain up to 2 weeks in 70% of patients [6, 7]. After cardiac surgery, concerns are raised regarding NSAID use with potential side effects (acute kidney injury (AKI) and major bleeding) [3, 8].

Recent recommendations advise against the use of NSAIDs after cardiac surgery due to the risk of renal impairment [3, 9]. This recommendation is based on a single-center study involving ibuprofen. Additionally, the effect on renal function was found to be of little significance. Additionally, clinical studies demonstrate that NSAID use is not associated with renal morbidity following cardiac surgery [10, 11].

Recently, we conducted a survey of practice regarding NSAID use in cardiac surgery revealing how heterogeny are the clinical practices [12]. Among respondents, and according the surgery type, from 44 to 87% of physicians declared using NSAIDs confirming a wide range among users. The discrepancy between the high rate of use of NSAIDs in the absence of recommendations for their use may be explained by the absence of literature on adverse effects in this indication.

Many studies support the safety use of NSAID in cardiac surgery regarding the risk of mortality, the risk of gastro intestinal ulcer, the risk of bleeding, or the risk of AKI. Also, we have several studies reporting NSAID safety, whether in terms of mortality, intestinal risk, thrombosis, AKI, or bleeding risk [5, 6, 8, 11, 13].

On the opposite, studies are scarce demonstrating the benefit on pain management in cardiac surgery [8, 10, 11].

Considering the beneficial effect of NSAIDs outside of cardiac surgery area and the lack of data on harmful effects, we hypothesize that NSAIDs have an appealing profile for this population.

However, to date, there is no randomized, double-blind, prospective study to conclude on the effect of NSAIDs in postoperative cardiac surgery. Our hypothesis is that NSAIDs are beneficial in terms of analgesia and without side effects, particularly regarding renal function.

Methods

Ethics and study design

The KETOPAIN trial is a prospective multicenter, randomized 1:1 ratio, double-blinded superiority, controlled trial (ClinicalTrials.gov, identifier: NCT06381063) of ketoprofen over placebo to treat postoperative pain after cardiac surgery under CPB. The protocol was approved by the Ethics Committee (Comité de Protection des Personnes Nord-Ouest III, 80,054 Amiens, France, registration number ID RDB: 2023–506299-28–00) on the 12th of March 2024 and by the ANSM (Agence Nationale de Sécurité du Médicament). The study design is detailed in Fig. 1. Flowchart is presented in Fig. 2. Study schedule is presented in Fig. 3 (SPIRIT figure). Written informed consent will be obtained from all participants or next of kin. The KETOPAIN Study will be conducted in accordance with the Declaration of Helsinki and French law on clinical research [14]. KETOPAIN trial protocol study follows the SPIRIT statement (Standard Protocol Items: Recommendations for Interventional Trials) [15].

Study population

The inclusion criteria are as follows:

- Patients more than 18 years old

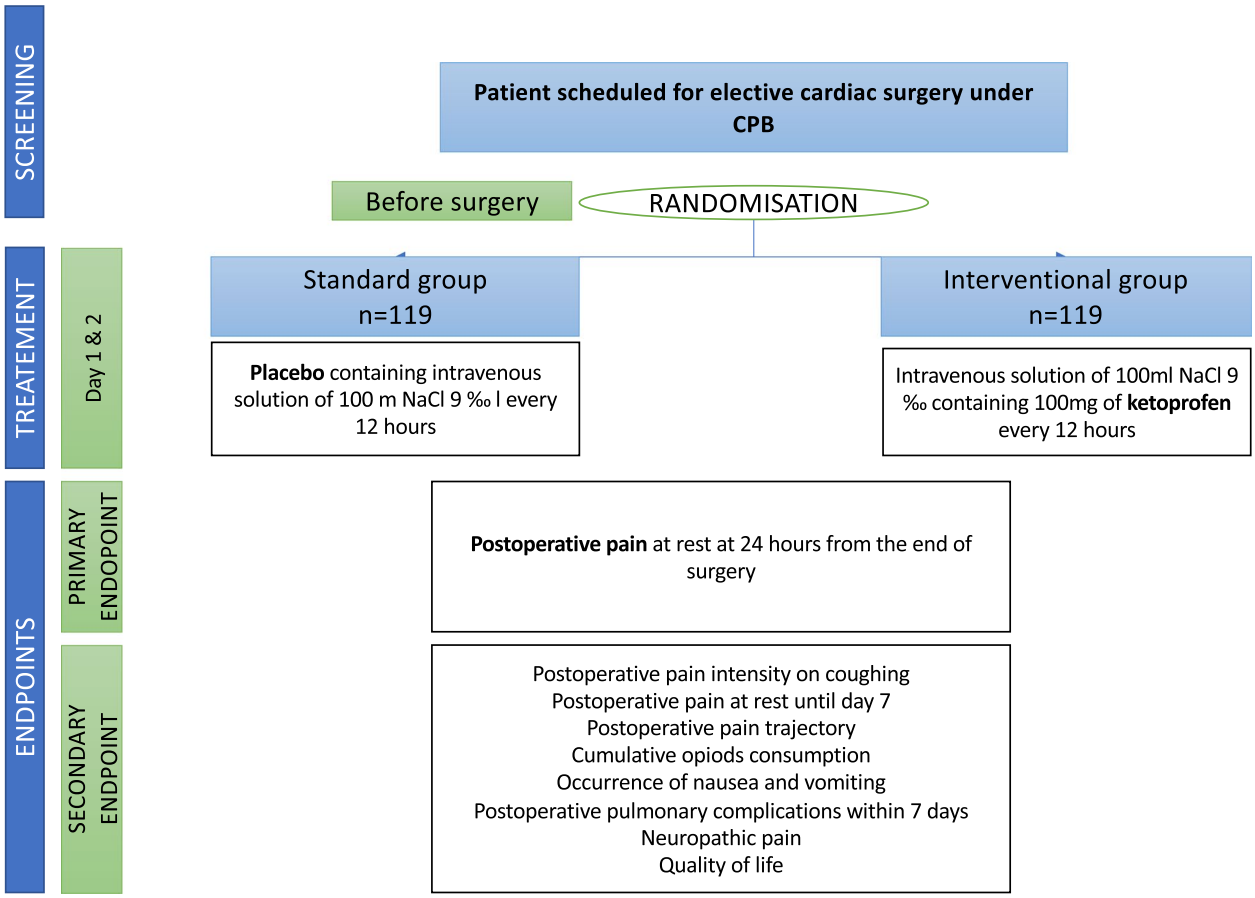

Fig. 1 Study design. CPB, cardiopulmonary by-pass

- Elective cardiac surgery under CPB
- Written informed consent from the patient or next of kin
- Highly effective contraception method for women of childbearing age

The non-inclusion criteria are as follows:

- Patient under 18 years of age
- Thoracotomy approach
- Minimally invasive approach
- Chronic NSAID use prior to surgery
- Opioid dependence or chronic opioid medication
- Emergency surgery
- Acute infective endocarditis
- Immunosuppressive or steroid treatment (prednisone > 0.5 mg·kg.$^{-1}$ per day or equivalent)
- AIDS with CD4 count < 200·mm.$^{-3}$
- Autoimmune disorder
- Transplant recipient
- Advanced chronic kidney disease (CKD 4 or 5)
- Renal replacement therapy within the last 90 days
- Depression with long-term treatment
- Patient on long-term tricyclic antidepressant or antiepileptic medication
- Pregnant or breast-feeding women
- Patient under guardianship or deprived of liberty
- Patient weighing less than 50 kg
- Contraindications to NSAID use: hepatic or renal insufficiency (eGFR < 60 ml·kg^{-1}·1.73 m^{-2}), documented thrombocytopenia (< 50.000·mm^{-3}), known allergy to NSAIDs, asthma triggered by NSAIDs, history of digestive hemorrhage or perforation during previous treatment with NSAIDs, cerebrovascular hemorrhage or other active hemorrhage, active peptic ulcer or severe cardiac insufficiency
- Contraindications to nefopam use: allergy, convulsions or history of convulsive disorders, risk of urinary retention due to urethroprostatic disorders, risk of angle-closure glaucoma
- Contraindications to acetaminophen use: allergy or severe hepatocellular insufficiency

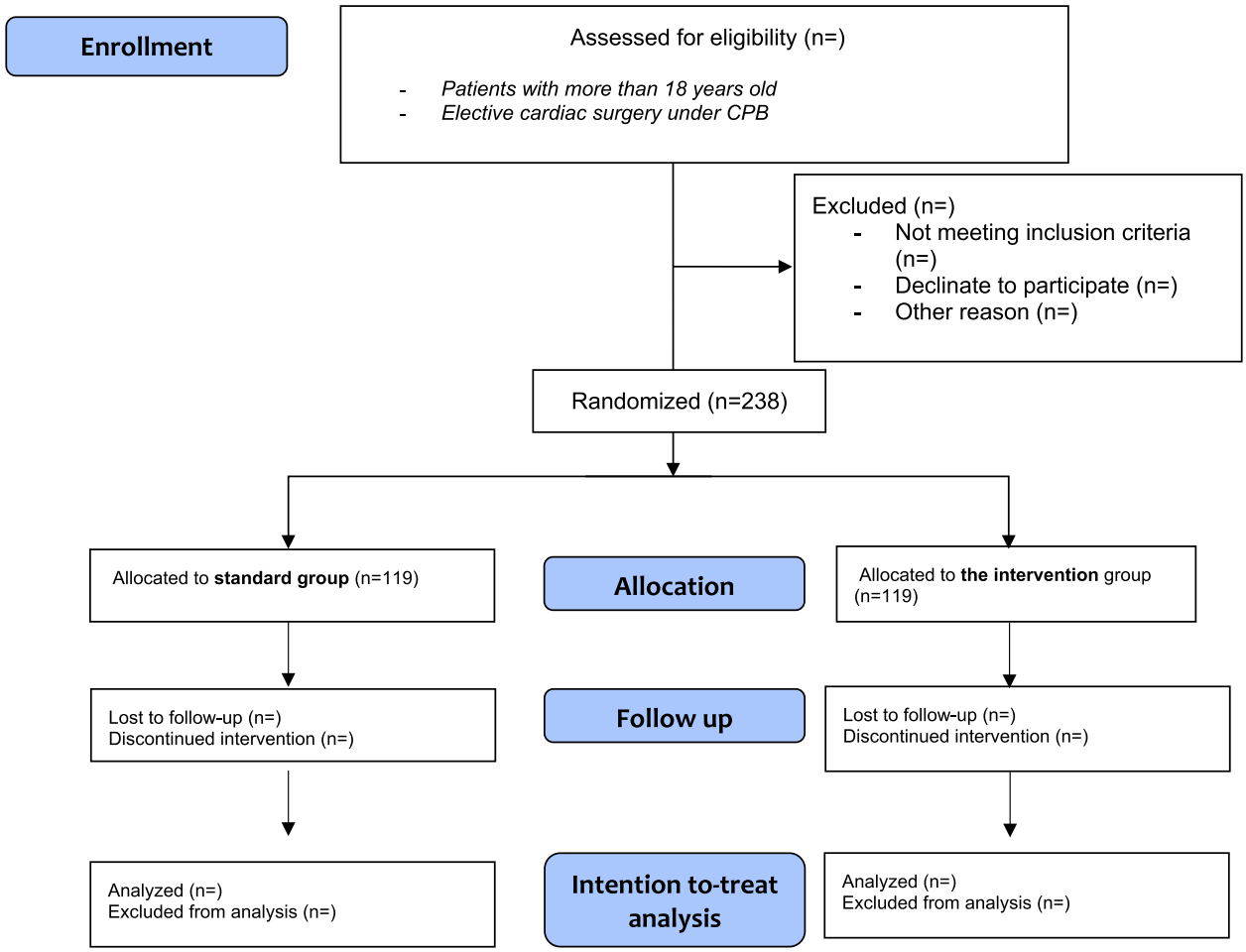

Fig. 2 Flowchart. CPB, cardiopulmonary bypass

– Contraindications to chloride sodium use: hyperchloremia, hypernatremia, severe cases of fluid retention

Study protocol

The number of centers participating in the study is 3 (Lille, Rouen, and Amiens cardiac surgery centers). Patients will be randomized into two parallel blinded groups. As the study is double-blind, investigators and patients will remain blind to treatment.

In the intervention group, patients will receive intravenous ketoprofen with 100 ml of NaCl 0.9‰ at a dose of 100 mg every 12 h for the 48 postoperative hours (i.e., 200 mg/day for 48 h).

In the control group, patients will receive a placebo of ketoprofen (100 ml of NaCl 0.9‰) with the same administration schedule as the interventional group, every 12 h for the 48 postoperative hours. The placebo planned in the study has no contraindication to its administration.

In both groups, in accordance with updated French recommendations on postoperative pain, pain management will be standardized for all patients (the 2 study groups) [2]. The pain relief protocol will include intraoperative administration of dexamethasone 8 mg and ketamine 0.5 $mg{\cdot}kg^{-1}$ after induction of anesthesia. During the first 48 h after surgery, the pain relief protocol will combine acetaminophen 1000 mg every 6 h, nefopam 20 mg every 8 h (6 doses), and ketoprofen or placebo as described above. In case of persistent pain with NRS > 3, initiate

	STUDY PERIOD									
	Enrolment	Allocation	Post-allocation							Close-out
TIMEPOINT	*Day before surgery*	V0 (Day 0)	*V1 (H+24)*	*V2 (H+48)*	*V3 (Day 3)*	*V4 (Day 4)*	*V5 (Day 5)*	*V6 (Day 6)*	*V7 (Day 7)*	*Month 3*
ENROLMENT:										
Eligibility screen	X									
Patient information	X	X								
Informed consent		X								
Randomization		X								
INTERVENTIONS:										
Intervention group KETOPROFEN		←	—	→						
Standard group PLACEBO		←	—	→						
ASSESSMENTS:										
Pain intensity at rest			X	X	X	X	X	X	X	
Pain intensity on coughing			X	X						
Pain trajectory assessment			X	X	X	X	X	X	X	
Cumulative opioids consumption			X	X						
Nausea and vomiting			X	X						
Pulmonary complication			X	X	X	X	X	X	X	
Neuropathic pain (DN4)				X						X
Quality of life scale (EQ-5D-5L)	X									X
Adverse events		X	X	X	X	X	X	X	X	X

Fig. 3 Schedule for enrolment, interventions, and assessments (SPIRIT figure)

morphine or oxynorm titration at 20 $\mu g \cdot kg^{-1}$ every 5 min until NRS ≤ 3 is achieved, followed by patient-controlled morphine analgesia (PCA morphine 1 mg/ml, no background infusion, bolus 1 mg, 7-min lockout). The treatment prohibited by the protocol is the administration of a 2nd NSAID in combination with the one prescribed in the study.

Anesthesia standardization

Patients will have perioperative management in accordance with the good practices of the French Society of Anesthesia and Intensive Care [3]. Discontinuation, continuation, or maintenance of the patient's chronic treatments follows international recommendations [3, 16]. Preoperative fasting is standardized for all patients: 2 h for clear liquids and 6 h for solid. The depth of anesthesia will be monitored with bispectral index s to target a value between 40 and 60. Ventilation will be set with a tidal volume between 6 and 8 $ml \cdot kg^{-1}$ of ideal weight, a respiratory rate to target an $EtCO_2$ between 30 and 40 mm Hg, and a positive end expiratory pressure at 5 cm H_2O. Anesthesia drug for induction (hypnotic drug, neuromuscular blocking agents, and opioid agents) will be chosen according to local habits. Transfusion is standardized across all centers and follow international recommendations on patient blood management [17]. Intraoperative and postoperative hemodynamic management is standardized for all patients. The objectives are a mean arterial pressure > 65 mm Hg and a cardiac index over 2.2 $ml \cdot min^{-1} \cdot m^{-2}$ [18]. Vasopressor, inotrope, and fluid use is guided by hemodynamic monitoring using echocardiography. Cardiopulmonary bypass will be managed according to international guidelines [19].

Outcome measures

The endpoints and definitions are presented in Table 1.

The primary endpoint will be the intensity of postoperative pain at rest at 24 h from the end of surgery using a numerous rating scale (NRS) graduated from 0 to 10 (see Appendix 1) [11].

The secondary endpoints will be:

– Postoperative pain intensity on coughing during chest physiotherapy (assessed using NRS) until day 2.

Table 1 Endpoints and definitions

Endpoints	*Definitions*
Primary endpoint at 24 h from the end of cardiac surgery	
Postoperative pain at rest at 24 h from the end of cardiac surgery	Postoperative pain at rest will be assessed at 24 h from the end of cardiac surgery using a numerous rating scale (NRS) graduated from 0 to 10 (see Appendix 1)
Secondary endpoints	
Postoperative pain intensity on coughing during chest physiotherapy	Postoperative pain intensity on coughing during chest physiotherapy (assessed using NRS) at day 1 and at day 2 from the end of cardiac surgery (see Appendix 1)
Postoperative pain at rest until day 7	Postoperative pain at rest will be assessed daily until day 7 using a numerous rating scale (NRS) graduated from 0 to 10 (see Appendix 1)
Postoperative pain trajectory	The pain trajectory will be assessed by taking into account the NRS between day 3 and day 7; a patient will be classified: "ideal" when NRS ≤ 4 from day 3 to day 7; "in late relief" when NRS > 4 on days 3, 4, or 5 and then NRS ≤ 4 on days 6 and 7; "in transient relief" when NRS ≤ 4 on day 3 to day 5 then > 4 on day 6 or 7; and "no relief" when NRS > 4 from day 3 to day 7
Cumulative opioid consumption	Cumulative consumption of morphine or oxycodone over 48 h, expressed in milligrams
Occurrence of nausea and vomiting	Occurrence of nausea (using a verbal scale: "none," "moderate," "severe") and number of vomiting will be recorded for 48 h
Postoperative pulmonary complications within 7 days after cardiac surgery	Evaluate the occurrence (within the first 7 days after cardiac surgery) of postoperative pulmonary complications according to European consensus definitions: respiratory infection, respiratory failure, atelectasis, bronchospasm
Respiratory infection	Antibiotics for suspected infection with one or more of the following: new or altered sputum, new or altered lung opacities, fever, white blood cell count > $12 \times 10^9 \cdot l^{-1}$
Respiratory failure	Postoperative PaO_2 < 60 mm Hg on room air, PaO_2/FiO_2 ratio < 300 mm Hg, or arterial oxyhemoglobin saturation measured by pulse oximetry < 90% and requiring oxygen therapy
Atelectasis	Pulmonary opacification with mediastinal displacement, hilum or hemidiaphragm displacement to the affected area, with compensatory hyperinflation in the adjacent non-atelectatic lung
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Neuropathic pain	Intensity of neuropathic pain at day 2 and month 3 using the Douleur Neuropathique questionnaire 4 (DN4) graded from 0 to 10 (see Appendix 2). Neuropathic pain will be defined as a DN4 > 3
Quality of life	Quality of life at 3 months will be assessed by the quality of life scale: EQ-5D-5L (see Appendix 3)

DN4 Douleur Neuropathique questionnaire, *NRS* Numerous rating scale

- The assessment of pain trajectory within 7 days after surgery. Pain trajectory will be defined according to NRS variation from day 3 to day 7 after surgery with four trajectories: "ideal," "in late relief," "in transient relief," and "no relief" [20].
- Cumulative opioid consumption for 48 h.
- Occurrence of nausea (using a verbal scale: "none," "moderate," "severe") and number of vomiting will be recorded for 48 h.
- Occurrence of a postoperative pulmonary complication within 7 days after cardiac surgery according to European consensus definitions [21, 22]:
  - Pneumonia (antibiotics for suspected infection with one or more of the following: new or altered sputum, new or altered lung opacities, fever, white blood cell count > $12 \times 10^9 \cdot l^{-1}$).
  - Acute respiratory failure (postoperative PaO_2 < 60 mm Hg on room air, PaO_2/FiO_2 ratio < 300 mm Hg, or arterial oxyhemoglobin saturation measured by pulse oximetry < 90% and requiring oxygen therapy).
  - Atelectasis (pulmonary opacification with mediastinal displacement, hilum or hemidiaphragm displacement to the affected area, with compensatory hyperinflation in the adjacent non-atelectatic lung).

- Bronchospasm (newly detected expiratory wheezing treated with bronchodilators).

– Neuropathic pain at day 2 and month 3 using the Douleur Neuropathique questionnaire 4 (DN4-questionnaire) graded from 0 to 10. Neuropathic pain will be defined as a DN4 > 3 (see Appendix 2) [2, 23, 24].
– Quality of life at 3 months assessed using the quality of life scale: EQ-5D-5L [25] (see Appendix 3).

Data collection and outcome definitions

The following data will be collected: age (years), gender, body mass index ($kg{\cdot}m^{-2}$), ASA score, logistic EuroSCORE, medical history (coronary disease, myocardial infarction, heart failure, pulmonary hypertension, atrial fibrillation, neurologic disorder, peripheral vascular disease, stroke, smoking, diabetes, dyslipidemia, chronic obstructive pulmonary disease, hypertension, chronic kidney disease (Cockcroft clearance < 60 ml/min), or sleep apnea syndrome), usual medication (antiplatelet therapy, anticoagulants, heart failure treatments, antihypertensives, glifozines, diuretics, antidiabetics, antiarrhythmics, or antilipemic drug) [26].

Preoperative biological parameters (hemoglobin, hematocrit, creatinemia, MDRD clearance, urea, ASAT, ALAT, troponin, CRP, protidemia, white blood cells, TP, APTT, fibrinogen, albuminemia) will be recorded. Surgery type (valve replacement, coronary bypass graft, or combined surgery), duration of CPB, and aortic clamp will be recorded. The anesthetic procedure includes the choice of anesthetic induction drugs with hypnotic (etomidate, propofol), mode of administration (bolus or target controlled infusion anesthesia), opioids (sufentanyl or remifentanyl), curare (cisatracurium or atracurium), and mode of maintenance (intravenous or inhaled). Cumulative doses will be collected.

Endpoints will be assessed after cardiac surgery.

Endpoints and definitions are presented in Table 1. The judging criteria will be defined and measured as defined above. Adverse events will be notified in the eCRFs. The investigator evaluates each serious adverse event from the date of signature of the consent form for up to 1 month, with no time limit if the adverse event is due to the investigational product or to the study procedure. The investigator notifies the sponsor and the clinical trials vigilance department of all serious adverse events occurring in participants within 24 h. Standard definitions of postoperative outcomes established by the European Society of Anesthesia will be used [22]. Cardiac arrest is defined as the cessation of cardiac mechanical activity, as confirmed by the absence of circulation signs. Stroke is defined as an embolic, thrombotic, or hemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g., hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) diagnosed on a cerebral scanner. AKI is defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine of over 27 µmol/l within 48 h or diuresis lower than 0.5 ml/kg/h [27]. Myocardial injury is diagnosed by the characteristics presentation, serial changes on 12-lead electrocardiographic suggesting infarction, and rise in cardiac troponin, with at least one value above the 99th percentile of the upper reference limit [28]. Mesenteric ischemia will be confirmed by imaging or exploratory laparotomy and ischemic colitis will be confirmed by gastrointestinal endoscopy or exploratory laparotomy. Perioperative bleeding will be defined according to the universal definition of perioperative bleeding (UDPB) [29]. The UDPB defines 5 perioperative bleeding classes (class 0 to class 4), which are designed to characterize the severity of bleeding.

Intention-to-treat analysis

Patients with serious adverse events will be analyzed according to their assigned group following the intention-to-treat principle.

Randomization

Patients will be randomized into two parallel blinded groups with a 1:1 ratio. Randomization will be performed using EnnovClinical® software, set up by a data manager from the Clinical Research and Innovation Department of Amiens-Picardie University Hospital. It will be a randomization by minimization, with stratification on center and sex (male, female). If no inconsistencies are found, the randomization result will display the treatment unit number to be assigned to the patient. As the study is double-blind, investigators and patients will remain blind to treatment. The placebo will be indistinguishable from the active drug. Unique package numbers for the trial drugs will be generated for both active and placebo products. Each treatment package will be numbered. The list of correspondence between the numbered packages and the nature of the treatments (ketoprofen/placebo) will be kept by the Methodology unit of the Amiens-Picardie University Hospital. A copy will be sent to the PUI of the CHU Amiens-Picardie.

Drug preparation, drug circuit, and blinding

Treatments will be supplied by the pharmacy of Amiens University Hospital, according to the specialties referenced at the time of the study: ketoprofen 100 mg (solution for infusion 100 ml, MACOPHARMA/CARELIDE or equivalent) and sodium chloride 0.9% (solution for infusion 100 ml, CARELIDE or equivalent). The bags of

solution for infusion are labeled with the research information (KETOPAIN Study). The primary packaging will not be modified. The bags will be packaged in a secondary container identified and sealed with a treatment number linked to the randomization in order to mask the contents. In this way, ketoprofen or sodium chloride is packaged in a neutral, labeled, and numbered container in order to maintain double blindness. These kits will be produced by the Amiens University Hospital pharmacy. Labeling will be carried out by Amiens University Hospital. Shipping and management of the products to the participating centers will be handled by the Amiens pharmacy. As the study is double-blind, investigators and patients will remain blind to treatment. The placebo will be indistinguishable from the active drug. Dispensing will be carried out by the center's pharmacy, 7 days a week. Once the treatment has been randomized and inserted, the nurse administers the treatment, and all used and unused kits are returned to the pharmacy at each center for accounting purposes. Statistical analysis will also be carried out on a blind basis.

Statistical method and sample size calculation

According to a previous randomized trial investigating pain after cardiac surgery by Rafiq et al. [13], the mean NRS was 3.5 ± 1.2 cm. Assuming a standard deviation of 2.3 cm and a percentage of 5% of patients not evaluable, we need to randomize 238 patients (119 per group) to detect a clinical difference of 1 cm for a 90% power and a two-sided alpha risk of 5%. The number of centers participating in the study is 3 (Lille, Rouen, and Amiens). The number of patients operated on per week was around 10 for Rouen and Amiens CHU and 30 for Lille CHU, i.e., around 50 patients per week operated on at the 3 centers. Inclusion of 3 patients per month per center seems to be a reasonable target, enabling us to reach a total of 238 patients over 3 years.

Statistical protocol will follow CONSORT guidelines for reporting parallel group randomized trials [30]. A flow chart will describe screened, randomized, and analyzed patients according to CONSORT guidelines. The main analysis will be an intention-to-treat analysis. No intermediate analysis is planned in the trial. For the description of the characteristics of the population, quantitative variables will be described by the mean ± standard deviation and the median (25th–75th). Qualitative variables will be described by their number (%). Comparison of pain between the two arms will be performed using an ANOVA model with adjustment for the initial pain value and stratification factors (center and gender). The α risk will be two-sided and set at 5%. Secondary end points will be assessed using an ANOVA test for repeated measures. Cumulative event curves will be estimated with the Kaplan–Meier procedure. Variables between usual and intervention groups will be compared with a Student test, a Wilcoxon-Mann–Whitney test, a chi-2 square, or a Fischer exact test as appropriate. We expect to observe very few missing data. Nevertheless, if any data are missing, they will be imputed using the multiple imputation technique with three replicates (predicted mean matching). The results of the three individual analyses will be merged using Rubin's method. Statistical analysis will be performed using SAS software version 9.4.

Data management and monitoring

Registration

Ethical authorization by the Comité de Protection des Personnes Nord-Ouest III, 80,054 Amiens, France, registration number ID RDB: 2023–506299-28–00 on the 12th of March 2024 and by the ANSM (Agence Nationale de Sécurité du Médicament). Registered on ClinicalTrials.gov on 24th April of 2024 (identifier: NCT06381063).

Data collection and management

Data collected directly from the patient will be entered into an electronic data capture database (eCRF). It will be stored on secure servers based at the lead organization. The databases will be password-protected and only accessible to specified and delegated trial individuals. Also, the sponsor is responsible to guarantee direct access to all research sites, source data, source documents, and reports for the purposes of quality control and audit by the sponsor. Investigators will make documents and individual data strictly necessary for the monitoring, quality control, and auditing of biomedical research available to persons with access to these documents in accordance with the legislative and regulatory provisions in force. As the risk associated with the use of NSAIDs is hypothetical and literature invalidate this risk, we have decided not to set up an independent monitoring committee.

Confidentiality

All persons involved will take all necessary precautions to ensure data confidentiality (patient identity and results obtained). Data confidentiality is ensured by pseudo-anonymizing patient information with the initials of the surname and first name and with a 5-digit code number (2 digits corresponding to the center number and 3 digits corresponding to the inclusion number).

Auditing

An audit may be carried out at any time and may apply to all stages of the research, from protocol development to publication of results and classification of data used or produced in the course of the research.

Study organization, trial intervention

The study promotion is performed by the University Hospital of Amiens, France. Ketoprofen is well tolerated, so we expect good compliance with the protocol. Subjects may withdraw their consent and ask to leave the study at any time, for any reason. The investigator may permanently discontinue a subject's participation in the study in the event of serious adverse events. Vigilance unit will remove the blind in case of serious unexpected adverse event.

Duration and timeline

Length of inclusion period will be 3-year period beginning before the end of the year 2024. Duration of each patient's participation will be 3 months. The database should be closed after all participants have been included, followed by data analysis, manuscript writing, and submission for publication.

Dissemination policy

Data analysis is carried out by the sponsor. The aim of this work is a scientific publication. Patients are informed, at their request, of the overall results of the research. The publication mentions the name of the sponsor, the investigators, the methodologists, the biostatisticians, and data managers who participated in the research.

Record keeping

Consent forms and eCRFs will be retained for 15 years at the University Hospital of Amiens in accordance with French law.

Discussion

The aim of this multicenter, randomized, placebo-controlled study is to improve pain management and postoperative recovery after cardiac surgery. If successful, NSAIDs could form part of a multimodal pain management regimen, as it has been demonstrated in major non-cardiac surgery.

Concerns about NSAIDs in cardiac surgery are related to the potential adverse effects, including thrombotic risk, AKI risk, and bleeding risk. Numerous studies support the possible use of NSAIDs in cardiac surgery without risk to the patient [5, 6, 8, 10, 11, 13].

A meta-analysis involving 5800 patients post-coronary bypass surgery demonstrated that NSAIDs do not elevate the risk of mortality, bypass thrombosis or stroke within 30 days following the procedure [6]. Also, in a monocentric randomized study including 182 patients, Qazi et al. showed no deleterious effects regarding sternal healing, postoperative bleeding, postoperative myocardial infarction or gastrointestinal bleeding [8]. Indeed, cardiac surgery is a surgery with a high bleeding risk of multifactorial origin [10]. NSAIDs could modulate renal blood flow, with afferent vasodilatation [31]. The incidence of AKI after cardiac surgery is 30% [32]. In this context, NSAIDs are often proscribed, even though clinical data show no increased risk [10, 11]. The risk of AKI can vary significantly based on patient and surgical risk factors and involves ischemia–reperfusion injury, inflammation, and changes in hemodynamics [33]. Hence, a cautious approach might entail contemplating NSAID utilization in patients with a low risk of AKI, while adhering to contraindications, and coupled with diligent monitoring of postoperative renal function.

Also, NSAIDs have been implicated in increasing the risk of myocardial infarction, particularly with high doses and prolonged exposure [34]. However, the utilization of NSAIDs after cardiac surgery has not been linked to myocardial injuries or bypass thrombosis or death 30 days after surgery [6].

Cardiac surgery is a high-risk surgery in terms of bleeding, which is caused by a number of factors (coagulopathy induced by CPB, antiplatelet agents, heparin, induced thrombopathy) [10]. Theoretically, NSAIDs may increase the risk of postoperative bleeding (modulation of COX, particularly COX2 with inhibiting platelet aggregation). However, the literature shows no clinical association between NSAIDs and postoperative bleeding [10].

In order to draw conclusions regarding the effectiveness of NSAIDs on postoperative pain in cardiac surgery, with the absence of adverse effects (particularly AKI), we have decided to conduct a prospective, multicenter, double-blind, randomized controlled trial.

Trial status

The trial is not yet recruiting. Protocol version number is 1.4, dated 12th of March 2024.

We aim to begin recruitment at the end of 2024 and we estimate the end of inclusions in late 2027.

Abbreviations

AIDS	Acquired-immune-deficiency-syndrome
AKI	Acute kidney injury
COX	Cyclooxygenase
CPB	Cardiopulmonary bypass
CKD	Chronic disease
eCRFs	Electronic case report forms
ICU	Intensive care unit
IRB	Institutional review board
KDIGO	Kidney Disease Improving Global Outcomes
NRS	Numerous rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
RRT	Renal replacement therapy
STS-SCA	Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists
SOFA	Sepsis-related Organ Failure Assessment

UDPB Universal definition of postoperative bleeding

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08326-z.

Additional file 1: Appendix 1. Numerous rating scale (NRS).

Additional file 2: Appendix 2. DN4-questionnaire.

Additional file 3: Appendix 3. Quality of life scale (EQ-5D-5L).

Additional file 4: SPIRIT checklist for *Trials*.

The trial management group

The trial management group is responsible for contributing to the design, coordination, and day-to-day operational and strategic management of the trial. This group is made up of the coordinating investigator, associate investigators, a trial methodologist, a statistician, a trial manager, a trial pharmacist, and qualitative researchers. There is no Trial Steering Group or stakeholder/public involvement group.

Amendments

Any substantial modification is the subject of a written amendment submitted to the sponsor, who must obtain a favorable opinion from the Ethics Committee and authorization from the ANSM prior to its implementation.

Sponsor

Promotor (sponsor) of study is Amiens Hospital University, 80,054 Amiens, France.
Ancillary and post-trial care.
There is no anticipated harm and compensation for trial participation. All post-trial care will be standard post-cardiac surgery care.

Authors' contributions

PH and OAA participated in the design of the study and helped to write the manuscript. MM, TL, GB, MG, CV, GH, SB, TC, SST, SB, HYA, PT, OF, CB, YM, HD, and EB participated in the design of the study. MD will perform the statistical analysis. All authors read and approved the final manuscript. Sponsor and funder have no role in study design.

Funding

The KETOPAIN trial received a French public grant from Programme Hospitalier Recherche Clinique interregional (PHRC interregional KETOPAIN # API 21–01).

Availability of data and materials

Data from the study will be made available at the end of the trial, on request.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Ethics Committee (Comité de Protection des Personnes Nord-Ouest III, 80054 Amiens, France, registration number ID RDB: 2023–506299-28–00) on the 12th of March 2024 and by the ANSM (Agence Nationale de Sécurité du Médicament). Written informed consent will be obtained from all participants or next of kin. Registered on ClinicalTrials.gov on 24th April of 2024 (identifier: NCT06381063).
SPIRIT checklist for *Trials* was used to draft this manuscript.

Consent for publication

Not applicable. No identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Anesthesia and Critical Care, Amiens Hospital University, 1 Rue du Professeur Christian Cabrol, Amiens 80054, France. [2]Department of Anesthesia and Critical Care, Lille Hospital University, Lille 59037, France. [3]Department of Statistic, Amiens Hospital University, Amiens 80054, France. [4]Department of Cardiac Surgery, Amiens Hospital University, Amiens 80054, France. [5]Clinical Research Centre, Amiens Hospital University, Amiens 80054, France. [6]Department of Pharmacology, Amiens Hospital University, Amiens 80054, France. [7]Faculty of Medicine, Department of Anesthesia and Critical Care, University of Jeddah, Jeddah, Saudi Arabia. [8]UR UPJV 758 SSPC (Simplification of Care of Complex Surgical Patients) Research Unit, University of Picardie Jules Verne, Amiens 80054, France. [9]Department of Anesthesia and Critical Care, Rouen Hospital University, Rouen 76031, France. [10]MP3CV, EA7517, CURS, Jules Verne University of Picardie, Amiens, France.

Received: 14 May 2024 Accepted: 8 July 2024
Published online: 16 September 2024

References

1. Devin CJ, McGirt MJ. Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes. J Clin Neurosci. 2015;22(6):930–8.
2. Aubrun F, Nouette-Gaulain K, Fletcher D, Belbachir A, Beloeil H, Carles M, et al. Revision of expert panel's guidelines on postoperative pain management. Anaesth Crit Care Pain Med. 2019;38(4):405–11.
3. Carillion A, Rozencwajg S, Abou Arab O, Fischer MO, SoMe Team of ACCPM. Enhanced recovery after cardiac surgery under CPB or off pump. Anaesth Crit Care Pain Med. 2022;41(4):101106.
4. Wick EC, Grant MC, Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. JAMA Surg. 2017;152(7):691.
5. Kulik A, Ruel M, Bourke M, Sawyer L, Penning J, Nathan H, et al. Postoperative naproxen after coronary artery bypass surgery: a double-blind randomized controlled trial. Eur J Cardiothorac Surg. 2004;26(4):694–700.
6. de Souza BF, Mehta RH, Lopes RD, Harskamp RE, Lucas BD, Schulte PJ, et al. Nonsteroidal anti-inflammatory drugs and clinical outcomes in patients undergoing coronary artery bypass surgery. Am J Med. 2017;130(4):462–8.
7. Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. Anesthesiology. 2006;105(4):794–800.
8. Qazi SM, Sindby EJ, Nørgaard MA. Ibuprofen - a safe analgesic during cardiac surgery recovery? A randomized controlled trial. J Cardiovasc Thorac Res. 2015;7(4):141–8.
9. Engelman DT, Ben Ali W, Williams JB, Perrault LP, Reddy VS, Arora RC, et al. Guidelines for perioperative care in cardiac surgery: enhanced recovery after surgery society recommendations. JAMA Surg. 2019;154(8):755.
10. Bainbridge D, Cheng DC, Martin JE, Novick R, Evidence-Based Perioperative Clinical Outcomes Research (EPiCOR) Group. NSAID-analgesia, pain control and morbidity in cardiothoracic surgery. Can J Anaesth. 2006;53(1):46–59.
11. Hynninen MS, Cheng DC, Hossain I, Carroll J, Aumbhagavan SS, Yue R, et al. Non-steroidal anti-inflammatory drugs in treatment of postoperative pain after cardiac surgery. Can J Anaesth déc. 2000;47(12):1182–7.
12. Abou-Arab O, Yakoub-Agha M, Moussa MD, Mauriat P, Provenchère S, Fellahi JL, et al. Nonsteroidal antiinflammatory drugs used in cardiac surgery: a survey of practices and new insights for future studies. J Cardiothorac Vasc Anesth. 2024;38(1):349–51.
13. Rafiq S, Steinbrüchel DA, Wanscher MJ, Andersen LW, Navne A, Lilleoer NB, et al. Multimodal analgesia versus traditional opiate based analgesia after cardiac surgery, a randomized controlled trial. J Cardiothorac Surg déc. 2014;9(1):52.
14. Toulouse E, Masseguin C, Lafont B, McGurk G, Harbonn AA, Roberts J, et al. French legal approach to clinical research. Anaesth Crit Care Pain Med. 2018;37(6):607–14.

15. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
16. Bloc S, Alfonsi P, Belbachir A, Beaussier M, Bouvet L, Campard S, et al. Guidelines on perioperative optimization protocol for the adult patient 2023. Anaesth Crit Care Pain Med. 2023;42(4): 101264.
17. Pagano D, Milojevic M, Meesters MI, Benedetto U, Bolliger D, von Heymann C, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. Eur J Cardio Thorac Surg. 2018;53(1):79–111.
18. Abou-Arab O, Huette P, Martineau L, Beauvalot C, Beyls C, Josse E, et al. Hyperoxia during cardiopulmonary bypass does not decrease cardiovascular complications following cardiac surgery: the CARDIOX randomized clinical trial. Intensive Care Med. 2019;45(10):1413–21.
19. Wahba A, Milojevic M, Boer C, De Somer FMJJ, Gudbjartsson T, van den Goor J, et al. 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. Eur J Cardiothorac Surg. 2020;57(2):210–51.
20. Vasilopoulos T, Wardhan R, Rashidi P, Fillingim RB, Wallace MR, Crispen PL, et al. Patient and procedural determinants of postoperative pain trajectories. Anesthesiology. 2021;134(3):421–34.
21. Fischer MO, Brotons F, Briant AR, Suehiro K, Gozdzik W, Sponholz C, et al. Postoperative pulmonary complications after cardiac surgery: the VENICE international cohort study. J Cardiothorac Vasc Anesth. 2022;36(8 PT A):2344–51.
22. Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol févr. 2015;32(2):88–105.
23. Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, et al. Development and validation of the neuropathic pain symptom inventory. Pain avr. 2004;108(3):248–57.
24. Beloeil H, Sion B, Rousseau C, Albaladejo P, Raux M, Aubrun F, et al. Early postoperative neuropathic pain assessed by the DN4 score predicts an increased risk of persistent postsurgical neuropathic pain. Eur J Anaesthesiol. 2017;34(10):652–7.
25. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res déc. 2011;20(10):1727–36.
26 Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41(4):734–44 (discussion 744-745).
27. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-184.
28. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019;40(3):237–69.
29. Dyke C, Aronson S, Dietrich W, Hofmann A, Karkouti K, Levi M, et al. Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg mai. 2014;147(5):1458-1463.e1.
30 Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2011;9(8):672–7.
31. Schjerning AM, McGettigan P, Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. Nat Rev Cardiol sept. 2020;17(9):574–84.
32. Just IA, Alborzi F, Godde M, Ott S, Meyer A, Stein J, et al. Cardiac surgery–related acute kidney injury _ risk factors, clinical course, management suggestions. J Cardiothorac Vasc Anesthes. 2022;36(2):444–51.
33. Von Groote T, Sadjadi M, Zarbock A. Acute kidney injury after cardiac surgery. Curr Opin Anaesthesiol. 2024;37(1):35–41.
34 Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, et al. Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. BMJ. 2017;357:j1909.

Publisher's Note