Journal of Cardiothoracic and Vascular Anesthesia 000 (2026) 1–10

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Evaluation of the Effect of Intravenous Lidocaine on the Systemic Inflammatory Response Associated With Cardiopulmonary Bypass in Valvular and/or Coronary Cardiac Surgery: Protocol for a Double-Blind Randomized Clinical Trial

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Objectives: To assess whether intravenous lidocaine reduces the systemic inflammatory response associated with cardiopulmonary bypass (CPB) and improves clinical outcomes in adult patients undergoing elective valvular and/or coronary cardiac surgery.
Design: Single-center, parallel-group, double-blind, randomized clinical trial.
Setting: San Pedro University Hospital, Logroño, Spain.
Participants: Ninety adult patients (≥18 years) scheduled for elective valvular and/or coronary surgery with CPB who provide informed consent.
Interventions: Patients will be randomly assigned to receive either intravenous lidocaine (1.5-mg/kg bolus followed by 1.5-mg/kg/h infusion until sternal closure) or an equivalent volume of saline solution as placebo. For patients with a body mass index greater than 30 kg/m^2, the

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https://doi.org/10.1053/j.jvca.2026.01.008

infusion dose will be adjusted according to ideal body weight, calculated as height (in centimeters) − 100 for men and height (in centimeters) − 110 for women.

Measurements and Main Results: The primary outcome is the interleukin 6 level at 6 hours postoperatively. Secondary outcomes include trajectories of inflammatory and myocardial injury biomarkers (C-reactive protein, high-sensitivity troponin T, and tumor necrosis factor α), postoperative complications related to the systemic inflammatory response (acute kidney injury, transfusion requirements, vasoplegia, respiratory dysfunction, delirium, infection, and multiorgan dysfunction), postoperative pain, intensive care unit length of stay, 30-day mortality, and incidence of post-CPB atrial fibrillation. The analysis will be conducted on an intention-to-treat basis.

Conclusions: This trial will determine whether intravenous lidocaine attenuates the systemic inflammatory response induced by CPB and improves clinical outcomes in adult patients undergoing elective cardiac surgery.

Key Words: systemic inflammation; cardiac surgery; intravenous lidocaine; cardiopulmonary bypass (CPB); myocardial injury; randomized controlled trial

CARDIOPULMONARY BYPASS (CPB) is one of the significant contributors to the systemic inflammatory response during cardiac surgery. This biological cascade results from the exposure of blood to artificial surfaces, ischemia-reperfusion injury following aortic cross-clamp removal, and endotoxemia.[1,2] Surgical trauma, mechanical ventilation, and blood product transfusion also contribute to the activation of this inflammatory response. In fact, procedures that avoid CPB, such as off-pump coronary artery bypass grafting, also trigger significant inflammatory cascades, and differences in outcomes between techniques such as transcatheter aortic valve implantation versus open surgery cannot be solely attributed to the use of extracorporeal circulation. CPB activates multiple inflammatory pathways, including complement activation (alternative and lectin pathways), the release of damage-associated molecular patterns, the release of proinflammatory cytokines (interleukin [IL] 6, IL-8, tumor necrosis factor α [TNF-α]), and the activation of leukocytes and adhesion molecules, all of which contribute to postoperative organ dysfunction.[2] A critical element in this cascade is the degradation of the endothelial glycocalyx, whose integrity is compromised by both prolonged CPB and nonspecific surgical factors such as mechanical trauma, turbulent flow, and hemodynamic fluctuations. These stimuli, compounded by ischemia-reperfusion injury, trigger the production of reactive oxygen species and the activation of proteases and heparanases, mediated by the release of adenosine and inosine. This proinflammatory environment induces the shedding of structural components such as syndecan-1 and heparan sulfate. Furthermore, perioperative splanchnic hypoperfusion facilitates endotoxin translocation, aggravating the systemic response and correlating with the degree of cardiovascular dysfunction. Because regeneration of the endothelial glycocalyx can take several days, its early protection and stabilization are essential to mitigate inflammation and prevent organ injury.[3,4]

These mechanisms can lead to systemic inflammatory response syndrome (SIRS) with significant perioperative complications, such as vasoplegic syndrome, myocardial dysfunction, or multiorgan failure.[2,5-7] Although various pharmacologic strategies and techniques have been proposed to attenuate this response, none has demonstrated consistent efficacy or become a consolidated standard of care.[8-11] Nonetheless, recent meta-analyses suggest that specific therapies, such as hemoadsorption, may reduce 30-day mortality and intensive care unit (ICU) length of stay in selected high-risk populations.[12] Despite these advances, the management of the inflammatory response remains a persistent clinical challenge.

Intravenous lidocaine, in addition to its analgesic and antiarrhythmic properties,[13,14] possesses membrane-stabilizing and anti-inflammatory effects that could mitigate endothelial degradation by suppressing leukocyte activation and decreasing proinflammatory mediators.[15,16] While its benefits in reducing the inflammatory response and improving functional recovery have been documented in noncardiac surgery,[17-19] evidence in the context of CPB remains limited. Preliminary studies suggest cytoprotective effects and a possible reduction in reperfusion-associated ventricular fibrillation.[18,20] Previous research, such as the work by Klinger et al.,[20] focused primarily on focal transcerebral activation, while other authors have explored gene expression through cardioplegia solutions.[21] The LEONARD trial addresses these limitations by implementing a more robust methodologic framework, including a standardized systemic intravenous infusion protocol, a calculated sample size to ensure statistical power, and a comprehensive 5-point kinetic evaluation of both inflammatory cytokines and myocardial injury markers. Fundamentally, this design allows for the correlation of the immunomodulatory response with critical inflammation-mediated postoperative complications—such as vasoplegia, organ dysfunction, and prolonged hospital stay—providing a comprehensive view of the potential clinical benefit of lidocaine.

Given the clinical burden associated with SIRS and the safety profile of lidocaine,[14,18,22,23] a randomized clinical trial is justified to evaluate its effect on inflammatory markers and associated postoperative complications. Because current standard care does not include a specific systemic anti-inflammatory treatment, normal saline solution was selected as a comparator to isolate the effects of lidocaine while maintaining blinding. Within this framework, the primary objective of this trial is to determine whether intraoperatively administered intravenous lidocaine can reduce the systemic inflammatory response associated with CPB in valvular and/or coronary cardiac surgery and its associated complications.

Objectives

The primary objective is to evaluate whether the perioperative administration of intravenous lidocaine reduces plasma levels of IL-6 at 6 hours after the completion of surgery in patients undergoing elective cardiac surgery (valvular and/or coronary) with CPB. As secondary objectives, the following parameters will be compared between the lidocaine group and the placebo group: Regarding the trajectories of biomarkers, levels of IL-6, TNF-α, C-reactive protein (CRP), and troponin T will be compared between the 2 groups at 5 specific time points: baseline (prior to anesthetic induction), start of CPB, end of surgery, 6 hours postoperatively, and 24 hours postoperatively. In terms of postoperative complications, the study will determine whether lidocaine reduces the incidence of complications associated with the systemic inflammatory response during the ICU stay, including acute kidney injury (Kidney Disease: Improving Global Outcomes [KDIGO] criteria), infection or sepsis, requirement for blood product transfusion, multiorgan dysfunction (Sequential Organ Failure Assessment [SOFA] score), vasoplegia (requirement for vasopressor support), and respiratory or neurologic dysfunction.

Furthermore, all-cause mortality at 30 days after surgery and total ICU length of stay will be compared between groups. A subgroup analysis will also be performed for all primary and secondary outcomes, stratifying the sample into coronary artery bypass grafting versus valvular and combined (valvular and coronary) surgery. Regarding electrophysiological effects, the study will determine whether lidocaine reduces the incidence of ventricular fibrillation and the need for internal defibrillation following aortic cross-clamp removal. Finally, the analgesic effect will be evaluated by measuring total opioid consumption and the requirement for rescue analgesia during the first 48 hours postoperatively.

Methods

Design and Setting

This is a low-intervention, superiority, prospective, randomized (1:1 ratio), double-blind, placebo-controlled clinical trial that will be conducted at a tertiary university hospital. The protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials [SPIRIT] 2013 guidelines. The study has been approved by the reference institutional review board and the relevant national regulatory authority. The trial is duly registered in national and European clinical trial databases under the registration number (2025-523534-11-00). Participants will be randomly assigned to one of the two study arms: lidocaine group (intervention) or placebo group (control).

Eligibility Criteria

Participant selection will be conducted following strict eligibility criteria to ensure sample homogeneity and subject safety. The study will include adult patients, aged 18 years and older, scheduled for elective cardiac surgery—including coronary artery bypass grafting, valve repair or replacement, or combined procedures—provided that the intervention requires the use of CPB. In all cases, the acceptance and signing of a written informed consent form after an adequate verbal and written explanation of the protocol will be required.

Conversely, patients presenting with factors that could interfere with the immunologic response or compromise the safety of the study drug will be excluded. Specifically, subjects with a history of hypersensitivity to lidocaine or amide-type local anesthetics will not be eligible, nor will those with severe organ dysfunction, defined as Child-Pugh class C hepatic impairment or severe renal failure with an estimated glomerular filtration rate of less than 30 mL/min.

Additionally, to avoid bias in the measurement of the inflammatory response, the study will exclude patients receiving chronic systemic corticosteroid treatment within the previous 90 days, those with an active infection requiring systemic antibiotic therapy or endocarditis during the current admission, and those who have experienced an acute coronary syndrome within 10 days prior to surgery. Furthermore, patients for whom the use of cytokine adsorption filters during CPB is anticipated will not be included, nor will pregnant or breastfeeding women or any case in which the patient's safety could be compromised under the clinical judgment of the principal investigator. Finally, any patient who experiences an anaphylactic reaction, who voluntarily withdraws consent, or in whom any of the aforementioned exclusion criteria develop will be withdrawn from the study.

Interventions and Perioperative Management

Participants will be randomly assigned to one of the two study arms in a 1:1 ratio. The lidocaine group will receive an initial intravenous bolus of 1.5 mg/kg during anesthetic induction, followed by a continuous intravenous infusion of 1.5 mg/kg/h. The selected dosage is based on the requirement to achieve stable plasma concentrations between 2 and 5 μg/mL. This range has been identified in the literature as optimal for obtaining immunomodulatory and membrane-stabilizing effects while maintaining a strict safety profile against local anesthetic systemic toxicity.[24,25] In obese patients (body mass index > 30 kg/m^2), the infusion dose will be adjusted to the ideal body weight—calculated using the sex-modified Broca formula—to prevent overdosing: height (in centimeters) − 100 for men and height (in centimeters) − 110 for women.[26]

The placebo group will receive a bolus and an infusion of 0.9% normal saline solution. To ensure the double-blind design, the pharmacy department will prepare both solutions in syringes and infusion sets with indistinguishable volume, color, and appearance. The infusion will be maintained throughout the surgical procedure and will be discontinued after sternal closure, prior to transfer to the ICU.

Anesthetic management will be conducted according to the institution's standard clinical practice. Induction will be performed with etomidate or propofol, and hypnotic maintenance will be achieved with sevoflurane. Neuromuscular blockade

will be maintained with rocuronium or cisatracurium, while the analgesic protocol will be based on remifentanil, fentanyl, and morphine hydrochloride. Tranexamic acid will be administered as antifibrinolytic therapy, and vasoactive or inotropic support (norepinephrine and dobutamine) will be provided according to individual hemodynamic requirements. Any deviation from the standard protocol prompted by the patient's clinical status will be prospectively recorded in the electronic case report form for subsequent analysis as a confounding variable.

Given the nature of the study drug, close surveillance for local anesthetic systemic toxicity will be performed. This will be based on the clinical detection of neurologic signs (paresthesia, metallic taste, tinnitus, altered level of consciousness, or seizure) and cardiovascular signs (bradycardia, refractory hypotension, or arrhythmia). Upon any reasonable suspicion of a serious adverse event related to the intervention, the infusion will be immediately discontinued, and the treatment code will be unblinded if necessary for clinical management.

To ensure the validity of the primary endpoint, CPB will be performed using a membrane oxygenator and non-pulsatile flow, maintaining the cardiac index and mean arterial pressure within physiological ranges according to the center's standardized management. Standardized priming volumes will be used to limit hemodilution. Likewise, conventional hemofiltration will be reserved exclusively for fluid balance control; the use of specific cytokine adsorption filters is excluded. Thermal management will be maintained between mild hypothermia and normothermia (34°C-37°C), and a restrictive transfusion strategy will be applied, with a hemoglobin threshold of 7.5 to 8 g/dL for the administration of packed red blood cells. The uniform application of these parameters in both study groups will minimize potential confounding factors.

During the ICU stay, the standard analgesic regimen will consist of intravenous paracetamol (1 g every 8 hours) and metamizole (2 g every 8 hours). In patients with an allergy to metamizole, intravenous tramadol (50 mg every 8 hours) should be used as an alternative. This regimen should be maintained during the first 48 postoperative hours, with additional opioid rescues permitted only in cases of insufficient pain control.

To prevent interference with the measurement of the inflammatory response, the administration of systemic corticosteroids and nonsteroidal anti-inflammatory drugs will be prohibited throughout the day of surgery. This restriction includes the preoperative period on the ward, anesthetic induction (specifically avoiding dexamethasone as an antiemetic) during the surgical procedure, and the first 24 postoperative hours. Additionally, locoregional blockade techniques will not be performed, nor will drugs with additional immunomodulatory or antiarrhythmic potential be used, such as dexmedetomidine, magnesium sulfate, or amiodarone. By restricting co-interventions to this standardized regimen, the study aims to ensure that observed changes in biomarkers are exclusively attributable to the intervention under study.

Variables

The study variables and their diagnostic frameworks are summarized in Table 1, with comprehensive definitions

Table 1
Summary of Study Variables: Definitions and Measurement Time Points

Category	Variable	Definition and Assessment Criteria	Measurement Timing
Primary outcome	IL-6	Plasma concentration (ECLIA)	T3
Secondary outcomes			
Inflammatory profile	IL-6, TNF-α, CRP, TnT	Sequential quantification to evaluate temporal trajectories and myocardial injury	T0, T1, T2, T3, T4
Complications	Acute kidney injury	KDIGO criteria	ICU stay
	Sepsis	Sepsis-3 criteria (confirmed infection + SOFA score ≥ 2)	ICU stay
	Multiple organ dysfunction	Dysfunction of ≥2 organ systems with SOFA score ≥ 2 for each system	ICU stay
	Postoperative vasoplegia	MAP < 65 mmHg + norepinephrine, 0.1 g/kg/min	ICU stay
	Respiratory dysfunction	PaO_2/FiO_2 ratio < 300 mmHg, invasive mechanical ventilation (>24 h), or reintubation	ICU stay
	Neurologic dysfunction	Delirium (confirmed by CAM-ICU scale) or stroke (ischemic or hemorrhagic, confirmed by CT or MRI)	ICU stay
	Blood product transfusion	Need for RBCs, FFP, platelets, or cryoprecipitate because of bleeding or hematologic thresholds	ICU stay
	Ventricular fibrillation	Incidence after aortic cross-clamp release; including number of shocks and electrical load required for sinus rhythm restoration	Intraoperative (after CPB)
	Opioid consumption	Cumulative morphine milligram equivalents and number of rescue doses required	First 48 h postoperatively
Long-term outcomes	Length of stay and mortality	Total ICU stay (in days) and all-cause mortality	Up to 30 d after surgery

CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; CPB, cardiopulmonary bypass; CRP, C-reactive protein; CT, computed tomography; ECLIA, electrochemiluminescence immunoassay; FFP, fresh frozen plasma; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IL, interleukin; KDIGO, Kidney Disease: Improving Global Outcomes; MAP, mean arterial pressure; MRI, magnetic resonance imaging; PaO_2, partial pressure of arterial oxygen; RBC, red blood cells; Sepsis-3, Third International Consensus Definitions for Sepsis and Septic Shock; SOFA, Sequential Organ Failure Assessment; T0, baseline (after induction); T1, start of cardiopulmonary bypass; T2, end of surgery (sternal closure); T3, 6 hours after surgery; T4, 24 hours after surgery; TNF, tumor necrosis factor; TnT, troponin T.

detailed herein. The primary outcome will be the plasma concentration of IL-6 at 6 hours after the completion of surgery (sternal closure), analyzed as a continuous quantitative variable.

In terms of secondary outcomes, the temporal trajectories of the inflammatory response and myocardial injury will be evaluated through sequential quantification of IL-6, TNF-α, CRP, and high-sensitivity troponin T. Blood samples will be obtained at 5 time points: baseline (after anesthetic induction), start of CPB, completion of surgery, 6 hours postoperatively, and 24 hours postoperatively.

The incidence of complications associated with the systemic inflammatory response during the ICU stay will be recorded, defined dichotomously (presence or absence) according to the following criteria:

- For renal dysfunction, acute kidney injury will be defined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (serum creatinine elevation $\geq$ 0.3 mg/dL within 48 hours or $\geq$1.5-fold increase from baseline or urine output $<$ 0.5 mL/kg/h for $>$6 hours).
- In terms of infection and sepsis, the criteria will consist of the presence of a confirmed or suspected infection meeting sepsis criteria (SOFA score $\geq$ 2 points or acute increase $\geq$ 2 points from baseline SOFA score) during the ICU stay, associated with clinical suspicion of infection. This suspicion is based on institutional clinical and microbiological surveillance protocols, including serial clinical evaluation and microbiological studies when indicated, allowing for robust differentiation between the sterile inflammatory response associated with surgery and an actual infection. The source of infection will be recorded if it is identified.
- Multiorgan dysfunction will be defined as dysfunction of 2 or more organ systems (cardiovascular, respiratory, renal, neurologic, hepatic, or hematologic) during the ICU stay, assessed using standardized scales such as the SOFA score, with a score of at least 2 points in at least 2 systems. Affected organs will be recorded.
- Regarding blood product transfusion, the need for transfusion support during the ICU stay will be recorded, defined as the administration of any blood product (packed red blood cells, fresh-frozen plasma, platelets, or cryoprecipitate) prompted by postoperative hemorrhage or laboratory levels of hemoglobin, platelets, and coagulation.
- The criteria for postoperative vasoplegia will consist of persistent hypotension with a mean arterial pressure lower than 65 mmHg despite adequate preload and—after ruling out myocardial dysfunction or active bleeding—requiring continuous norepinephrine administration at doses of at least 0.1 μg/kg/min during the ICU stay. Temporary adjustments of vasopressor support during weaning from CPB or those linked to transient hemodynamic maneuvers will not be considered vasoplegia.
- Respiratory dysfunction will consist of the presence of respiratory failure after admission and stabilization in the ICU, ensuring that this reflects postoperative clinical evolution and not acute intraoperative physiological alterations. It will be defined by a Kirby index, calculated as the arterial partial pressure of oxygen (PaO_2) divided by the fraction of inspired oxygen (FiO_2), below 300 mmHg, the need for prolonged invasive mechanical ventilation for more than 24 hours, or the requirement for reintubation after failed extubation.
- Neurologic dysfunction will consist of the presence of acute confusional syndrome (delirium) or a cerebrovascular event. The diagnosis of delirium should be based on systematic clinical evaluation using the validated Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Ischemic or hemorrhagic stroke will require confirmation via neuroimaging, such as cranial computed tomography or magnetic resonance imaging.

Analgesic efficacy during the first 48 postoperative hours will be evaluated through cumulative opioid consumption, expressed in milligrams of morphine equivalents, and the number of additional rescue doses required (analgesia outside the scheduled pharmacologic regimen). The total length of stay in the ICU, expressed in days from admission to discharge, will be analyzed, as well as all-cause mortality during the first 30 days after surgery. Additionally, the incidence of ventricular fibrillation immediately after aortic cross-clamp removal (following myocardial reperfusion) will be evaluated, recording the need for defibrillation to restore sinus rhythm, the number of shocks administered, and the electrical energy required.

Participant Timeline

The study schedule is summarized in Figure 1. The process will begin with recruitment and the procurement of informed consent, which will be conducted by a member of the anesthesiology department during the pre-anesthesia consultation or during hospital admission prior to the procedure. Once patient inclusion is formalized, the pharmacy department will be responsible for performing the randomization and preparing the study medication. The medication will be prepared a few hours before surgery to ensure the maintenance of blinding and the correct distribution of the drug or placebo.

The intervention and sampling protocol will commence on the day of surgery. A primary blood sample will be obtained from the arterial catheter before anesthesia induction to establish baseline values. During induction, the initial bolus of the study drug or placebo will be administered, followed by the initiation of the continuous intravenous infusion. Throughout the surgical procedure, blood samples will be drawn at the start of CPB and at the completion of surgery, following sternal closure. Additionally, data regarding ventricular fibrillation will be specifically recorded at the time of aortic cross-clamp removal.

During the postoperative period, arterial blood samples will be obtained at 6 and 24 hours. The collection of clinical data regarding complications in the ICU should extend from the time of transfer from the operating room until discharge from the unit. Finally, the follow-up will conclude with the assessment of postoperative pain during the first 48 hours and the

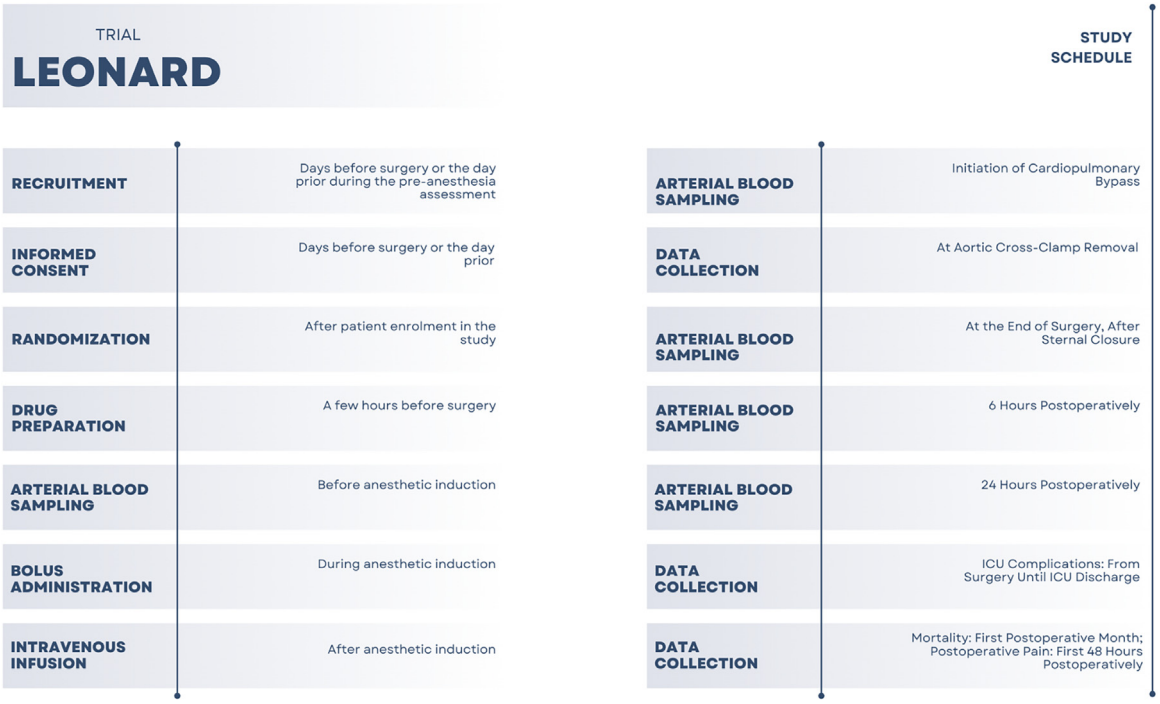

Fig 1. Study schedule showing key moments and interventions. ICU, intensive care unit. LEONARD, internal name in the clinical trial.

recording of mortality at 1 month following the surgical intervention.

Sample Size

The sample size was calculated to detect a clinically significant difference in IL-6 levels at 6 hours postoperatively between the intervention and control groups. In the absence of specific previous literature regarding the effect of lidocaine on the cytokine profile in this surgical context, dispersion parameters were estimated based on a landmark clinical trial investigating the impact of high-dose heparin on the inflammatory response associated with CPB.[27] On the basis of a median of 75 pg/mL and an interquartile range of 65 to 90 pg/mL, a mean of 75 pg/mL and a standard deviation of 18.5 pg/mL were estimated.

Under the aforementioned premises, assuming an α risk of 0.05 and a statistical power of 80% for a 2-sided test, it was determined that 44 subjects per group would be required to detect a difference of 12 pg/mL or greater in the primary outcome. To compensate for an estimated loss–to–follow-up rate of 15%, the final sample size was set at 90 patients, distributed equally into 2 groups of 45.

Given its design, this work is framed as a proof-of-concept study. Although the sample size is sufficient to identify significant differences in the primary biochemical marker, it is acknowledged that the power might be limited for evaluating secondary clinical outcomes. For this reason, clinical findings will be interpreted in an exploratory and cautious nature, aimed at establishing the methodologic foundations for future larger-scale clinical trials.

Recruitment

The invitation to participate in the study will be extended by a member of the anesthesiology department during the pre-anesthesia consultation or during hospital admission prior to surgery, once eligibility criteria have been verified. Patients will receive an informed consent document and will be provided with sufficient time to resolve any questions with the medical team, as well as to discuss the decision with their family or close relatives.

To ensure a consistent recruitment rate, the investigators will perform daily monitoring of the cardiac surgery department's surgical schedule. The recruitment process and the estimated progression of subjects through the study phases are schematically represented in Figure 2 (Consolidated Standards of Reporting Trials [CONSORT] flow diagram).

Randomization

Participants will be assigned to the study groups (lidocaine or placebo) through simple randomization with a 1:1 ratio. The allocation sequence will be generated and managed electronically using the specialized randomization module within the REDCap (Research Electronic Data Capture) platform.

To ensure the integrity of the trial, this sequence will be uploaded into the system by personnel independent of the research team. In this manner, the allocation will remain concealed from both the investigators responsible for recruitment and the personnel tasked with administering the treatment and evaluating the outcomes, ensuring the maintenance of the double-blind design throughout all phases of the study.

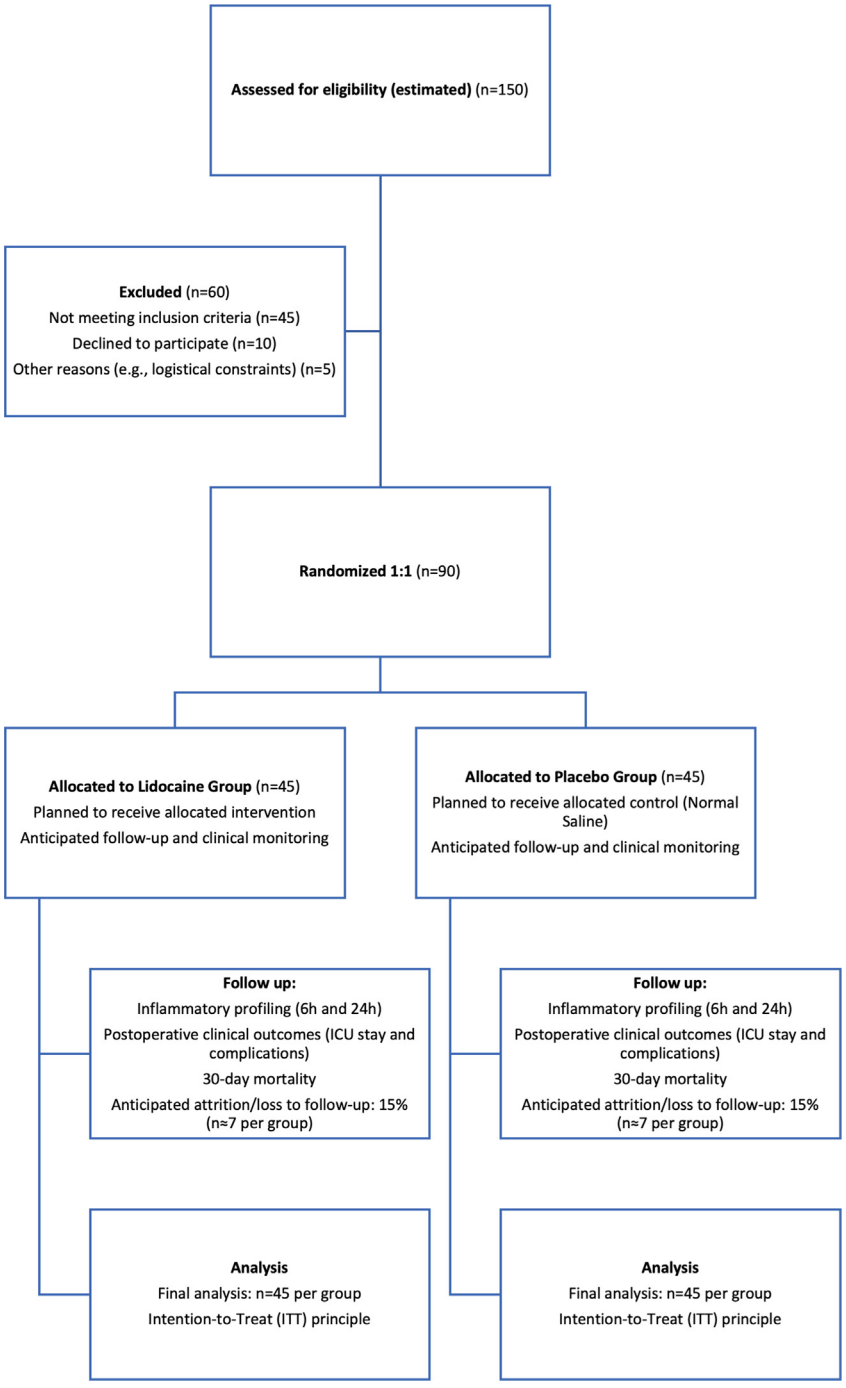

Fig 2. Prospective Consolidated Standards of Reporting Trials (CONSORT) flow diagram of study protocol. h, hours; ICU, intensive care unit.

Implementation and Blinding (Masking)

To ensure double blinding and minimize the risk of bias, treatment group allocation will be managed exclusively by the hospital's pharmacy department. Pharmacy personnel will be responsible for preparing the intravenous solutions of lidocaine or placebo (0.9% normal saline solution), ensuring that they are visually and physically indistinguishable (same color, volume, and type of syringe and container). Masking will extend to all levels of the study: patients, surgical and anesthetic teams, nursing staff, investigators, data collection personnel, laboratory technicians, and the statistician responsible for data analysis.

The anesthesia nursing staff or the anesthesiologist will be responsible for the intravenous administration of the study medication. Both lidocaine and placebo will be administered in identical volumes based on the patient's body weight.

To minimize the risk of clinical unblinding due to the potential hemodynamic or electrophysiological effects of lidocaine, patient management will follow standard clinical practice. This approach ensures that any drug-induced fluctuations are

indistinguishable from the physiological variability inherent to cardiac surgery and CPB.

In the event of a medical emergency in which knowledge of the assigned treatment is essential for patient safety, immediate unblinding by the investigator will be permitted. In such a situation, the patient will not necessarily be excluded from the study, and his or her data will be retained for intention-to-treat analysis, with corresponding sensitivity analyses performed if necessary.

Data Collection and Management

Data Management and Custody

Clinical and perioperative patient data will be collected in an electronic case report form within REDCap, ensuring pseudonymization and information confidentiality. Recorded data will include the variables previously described, as well as additional data such as relevant medical history, anthropometric measurements, duration of CPB and aortic cross clamping, occurrence of intraoperative cardiac events, and blood product transfusion.

All data will be reviewed by the research team to ensure completeness and accuracy. The storage and management of information will comply with local regulations regarding data protection and confidentiality in clinical research.

Biological Sample Collection and Processing

The sample collection schedule was designed to accurately characterize the kinetic profile of the perioperative inflammatory response. An initial sample (T0, baseline) will be obtained prior to anesthetic induction to establish the patient's starting inflammatory status. Subsequently, a sample (T1, start of CPB) will be drawn after sternotomy and at the initiation of CPB, allowing for the isolated quantification of inflammation attributable to surgical trauma and anesthetic techniques. The final intraoperative draw (T2, end of surgery) will be performed after complete sternal closure. In the postoperative period, the sample at 6 hours (T3) will be obtained to capture the predicted peak release of proinflammatory cytokines resulting from the systemic insult of CPB. Finally, the sample at 24 hours (T4) will be collected to evaluate the resolution phase or the peak of the inflammatory cascade and the evolution of acute-phase reactants. To ensure reproducibility, a tolerance margin of $\pm$15 minutes for intraoperative samples and $\pm$30 minutes for postoperative samples was established.

Sample processing will be conducted by qualified technical personnel, blinded to group allocation, and according to standardized laboratory procedures, using plasma or serum as specified for each biomarker. Standard quality control and periodic calibration protocols will be followed to ensure the reproducibility of the results.

For TNF-α analysis, one specific blood tube for serum collection will be drawn at each of the 5 study points. These samples will be kept refrigerated at 4°C to 5°C until they are sent to the biomedical research center. At the center, the blood will be processed to obtain serum through centrifugation at 3,000*g* for 10 minutes at 4°C. Samples will be coded to maintain patient confidentiality, aliquoted, and stored at −80°C until subsequent use. The measurement of serum TNF-α levels will be performed using an enzyme-linked immunosorbent assay test, specifically the Human TNF-alpha Quantikine HS ELISA from R&D Systems (Minneapolis, MN), following the manufacturer's instructions. TNF-α levels will be measured at all 5 study points.

CRP will be determined using an immunoturbidimetric method, in accordance with the standardized procedures of the hospital's central laboratory. IL-6 and high-sensitivity troponin T will be quantified with an electrochemiluminescence immunoassay using the validated platform available in the laboratory and its standard protocols.

The selection of biomarkers in this study is based on their critical role in SIRS following CPB. IL-6 and TNF-α are proinflammatory cytokines that rise rapidly after exposure to CPB; IL-6 reaches early peaks and has been established as a robust predictor of respiratory failure, renal dysfunction, and postoperative infectious complications.[28,29] Although TNF-α exhibits greater clinical variability, it is an essential mediator of endothelial damage and activation of the inflammatory cascade.[28,30] CRP, synthesized by the liver in response to IL-6, serves as a sensitive marker for monitoring the evolution and resolution of systemic inflammation in the days following surgery.[28,31] Finally, high-sensitivity troponin T is included as a specific indicator of myocardial injury, reflecting necrosis due to ischemia-reperfusion and inflammation-mediated damage, which directly correlates with cardiac prognosis.[31,32]

Statistical Methods

Statistical analysis will be conducted according to the intention-to-treat principle using R software, version 4.5.2, with the R Commander interface (R Foundation for Statistical Computing, Vienna, Austria). A clear distinction should be made between primary and secondary variables, using appropriate methods based on their nature and distribution. Baseline demographic and clinical characteristics for each group will be described using descriptive statistics: Quantitative variables will be expressed as mean and standard deviation or as median and interquartile range based on the Shapiro-Wilk test, whereas qualitative variables will be presented as absolute frequencies and percentages.

For comparisons between intervention groups, continuous variables will be analyzed using the Student t test or Mann-Whitney U test and categorical variables will be analyzed using the χ^2 test or Fisher exact test. Because biomarkers (IL-6, TNF-α, CRP, and troponin T) typically exhibit an asymmetrical distribution, a logarithmic transformation will be applied to satisfy normality assumptions. Their evolution across the 5 time points will be evaluated using linear mixed-effects models, which allow for the analysis of the effects of treatment, time, and their interaction, while adjusting for intra-subject correlation. The optimal covariance structure will be selected based on the lowest Akaike information criterion. Models will be adjusted for confounding factors such as

baseline values, surgery type, CPB duration, cross-clamp time, and intraoperative transfusion.

Additionally, the area under the curve will be calculated for all biomarkers using the trapezoidal rule from baseline to 24 hours. To control for type I errors resulting from multiple comparisons, the Bonferroni correction or the Benjamini-Hochberg method should be applied. Postoperative pain will be analyzed using the Mann-Whitney U test for opioid consumption, whereas ICU length of stay and 30-day mortality will be evaluated using the Kaplan-Meier method and Cox regression models.

Regarding missing data management, a complete-case analysis will be performed if the proportion is below 5%; otherwise, the multiple imputation by chained equations (MICE) technique will be performed under the assumption of data missing at random. For all analyses, a 2-tailed p value < 0.05 is considered statistically significant.

Monitoring

Because this is a low-intervention clinical trial—in which intraoperative lidocaine is administered at standard therapeutic doses and no interim analyses with early stopping rules are planned—an independent data monitoring committee will not be established. Nevertheless, the safety and integrity of the trial will be continually supervised by qualified personnel independent of the research team. This monitoring process will be conducted in strict compliance with current International Council for Harmonisation - Good Clinical Practice guidelines [ICH-GCP E6(R3)], ensuring the protection of participants' rights and the veracity of the collected data.

Ethical Considerations and Safety

The study has been approved by all relevant regulatory bodies. All procedures are conducted in accordance with the Declaration of Helsinki, Good Clinical Practice standards, the European Union Clinical Trials Regulation (No. 536/2014), and current national legislation. Written informed consent will be obtained from all participants prior to their inclusion. Data confidentiality is guaranteed through pseudonymization in REDCap, in compliance with current national regulations and the General Data Protection Regulation (EU No. 2016/679). Each participant will be assigned a unique code; the linking key will be stored independently with restricted access, ensuring that statistical analysis is performed exclusively on anonymized information. Master-file data will be preserved for a minimum period of 25 years following the conclusion of the study, after which they will be securely destroyed.

No financial compensation will be provided to study participants as participation is voluntary. No events requiring compensation or additional care after the trial are expected, given the well-established safety profile of lidocaine at therapeutic doses.

All adverse events will be recorded and reported following the pharmacovigilance procedures predefined in the protocol and the Clinical Trials Information System regulatory framework for low-intervention clinical trials. Patients may be withdrawn from the study if serious adverse reactions occur, if previously undetected exclusion criteria emerge, or by the participant's own decision.

The results of this study will be presented at scientific congresses and submitted for publication in international peer-reviewed journals, regardless of the nature of the findings, following the Consolidated Standards of Reporting Trials (CONSORT) guideline recommendations.

Administrative Information

Clinical Trial Title: Evaluation of the Effect of Intravenous Lidocaine on the Systemic Inflammatory Response Associated with Cardiopulmonary Bypass in Patients Undergoing Elective Valvular and/or Coronary Cardiac Surgery: Double-Blind Randomized Clinical Trial.

Trial Code: LEONARD Trial

The European Union Clinical Trials (EUCT) Registration: 2025-523534-11-00; registered on November 19, 2025.

National Clinical Trials Registry: registered on November 19, 2025.

Protocol version and date: No. 3; October 31, 2025

Data sharing statement: Individual participant data, the statistical code, and other study materials will be made available upon reasonable request from the corresponding author, subject to institutional approval and applicable data protection regulations.

Dissemination plans: The results of the trial will be submitted for publication in a peer-reviewed scientific journal. Summaries of the findings should also be communicated to participants and health care professionals in an understandable format. Key trial outcomes should be reported in the trial registries to ensure transparency and accessibility.

Principal investigator: The principal investigator is Ana Fernández Martínez, MD, PhD candidate, affiliated with the Hospital Universitario San Pedro, Logroño, Spain and the University of the Basque Country, Bilbao, Spain. Email: afernandez450@ikasle.ehu.eus.

Sponsor: The study sponsor is Ana Fernández Martínez, MD, PhD candidate, affiliated with the Hospital Universitario San Pedro, Logroño, Spain and the University of Basque the Country, Bilbao, Spain. Email: afernandez450@ikasle.ehu.eus..

Funding: No external funding has been received.

Ethical Approval

The study was approved by the La Rioja Drug Research Ethics Committee (CEImLAR, code EC-BNI 261) and by the Spanish Agency of Medicines and Medical Devices (AEMPS). All activities will be conducted in accordance with the principles of the Declaration of Helsinki and current Spanish regulations on clinical drug research. Any substantial modification to the research protocol will be submitted via the Clinical Trials Information System (CTIS) following current regulations.

Declaration of competing interest

All investigators involved in this trial declare no financial or other conflicts of interest.

CRediT authorship contribution statement

Ana Fernández-Martínez: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Amanda López Picado:** Writing – review & editing, Supervision, Methodology, Investigation. **Joseba González-García:** Writing – review & editing, Supervision, Methodology, Investigation. **Marta Aguado Sevilla:** Validation, Project administration, Methodology. **Félix Lobato Solores:** Project administration, Methodology. **Beatriz Castroviejo Ibáñez:** Project administration, Methodology. **Patricia de Miguel Fernández:** Project administration, Methodology. **Pilar Benito Martínez:** Project administration, Methodology. **Sara Valero González:** Project administration, Methodology. **Ana Isabel Galve Marqués:** Project administration, Methodology. **Isabel Mainar Gil:** Project administration, Methodology. **Nisa Boukichou Abdelkader:** Formal analysis, Data curation. **María Íñiguez Martínez:** Methodology, Investigation. **Adriana Bermejo Bravo:** Project administration, Investigation. **Rebeca Apiñaniz Apiñaniz:** Project administration, Investigation. **Esther Corral Cárdenas:** Project administration, Methodology. **Lourdes Ferreira Laso:** Conceptualization.

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