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ORIGINAL

The effect of local anesthetic continuous wound infusion for the prevention of postoperative pneumonia after on-pump cardiac surgery with sternotomy: the STERNOCAT randomized clinical trial

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Abstract

Purpose: Postoperative pain after cardiac surgery, exacerbated by cough and sternal mobilization, limits clearance of bronchopulmonary secretions and may predispose to postoperative pneumonia. In this study, we tested the ability of local anesthetic continuous wound infusion to prevent pneumonia after cardiac surgery with sternotomy and cardiopulmonary bypass (CPB) owing to better analgesia and bronchopulmonary drainage.

Methods: In this randomized, double-blind, placebo-controlled trial conducted in five academic centers, patients undergoing cardiac surgery with sternotomy and CPB were enrolled from February 2012 until November 2014, and were followed over 30 days. Patients were assigned to a 48-h infusion (10 ml h^{-1}) of L-bupivacaine (12.5 mg h^{-1}) or placebo (saline) via a pre-sternal multiperforated catheter. Anesthesia and analgesia protocols were standardized. The primary end point was the incidence of pneumonia during the study period, i.e., until hospital discharge or 30 days. We hypothesized a 30% reduction in the incidence of pneumonia.

Results: Among 1493 randomized patients, 1439 completed the trial. Pneumonia occurred in 36/746 patients (4.9%) in the L-bupivacaine group and in 42/739 patients (5.7%) in the placebo group (absolute risk difference taking into account center and baseline risk of postoperative pneumonia, − 1.3% [95% CI − 3.4; 0.8] $P = 0.22$). In the predefined subgroup of patients at high risk, L-bupivacaine decreased the incidence of pneumonia (absolute risk difference, − 5.6% [95% CI − 10.0; − 1.1], $P = 0.01$).

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Conclusions: After cardiac surgery with sternotomy, continuous wound infusion of L-bupivacaine failed to decrease the incidence of pneumonia. These findings do not support the use of local anesthetic continuous wound infusion in this indication. Further study should investigate its effect in high-risk patients.

Trial registration: EudraCT Number: 2011-003292-10; Clinicaltrials.gov Identifier: NCT01648777.

Keywords: Pneumonia, Cardiac surgery, Critical care medicine, Postoperative pain, Local anesthetics

Introduction

Pneumonia is a frequent complication in patients undergoing cardiac surgery with sternotomy and cardiopulmonary bypass (CPB) [1–5]. Although medical and surgical progress has consistently improved perioperative care, respiratory complications occur in 3–30% [1–4] and represent one of the main causes of morbidity and mortality after cardiac surgery [6]. Postoperative pneumonia increases the risk of prolonged mechanical ventilation, renal replacement therapy, intensive care unit (ICU) and total hospital lengths of stay, as well as mortality [2–4, 6].

After cardiac surgery with sternotomy, postoperative pain plays an important role in impaired pulmonary function [5, 7–10]. Usually moderate to severe at rest, pain intensity increases strongly with iterative chest mobilization due to cough, deep breathing, and during active chest physiotherapy [9]. Because of changes in pulmonary mechanical properties, the colonization of the tracheobronchial tree by bacteria can evolve towards pneumonia [2, 5, 11]. Uncontrolled postoperative pain leads to increased pain distress [10], opioid consumption and its side effects, and pulmonary complications [9, 11–13]. In this context, the use of local anesthetic continuous wound infusion [14, 15] through a multiperforated catheter within a multimodal analgesia strategy has been shown to improve postoperative analgesia after cardiac surgery with sternotomy [1, 14–17]. This therapeutic strategy may help to reduce the incidence of atelectasis and pulmonary disorders, offering the opportunity for better chest drainage and contributing to a decrease in the incidence of postoperative pneumonia.

The aim of this study was to test the ability of continuous wound infusion during the first 48 h of L-bupivacaine with multiperforated catheter to prevent postoperative pneumonia after cardiac surgery with sternotomy and CPB.

Methods

The study was approved by an independent National Research Ethics Committee (Comité de Protection des Personnes Ile de France VI; no. 83-11) and registered in EudraCT (2011-003292-10) and Clinicaltrials.gov (NCT01648777). The study protocol is available in the Online Supplement. The reporting of the study followed the Consolidated Standards of Reporting Trials (CONSORT) statement [18].

Take-home message

After cardiac surgery with sternotomy, continuous wound-infusion of L-bupivacaine slightly improves postoperative analgesia but does not reduce the incidence of pneumonia. These findings does not support the use of local anesthetic infusion in this indication.

Participants

Five academic cardiac surgical centers participated. Patients undergoing planned cardiac surgery with sternotomy and CPB were included after providing written informed consent.

Exclusion criteria were refusal to participate, age < 18 years, pregnancy, emergency surgery, patient in whom fast-track cardiac anesthesia was not expected, moribund state, palliative care, decision of limitation of care, preoperative pneumonia, participation in another randomized trial, lack of national health care insurance, and allergy.

Trial design and randomization

This trial was a randomized, double-blind, two-arm, parallel-group, multicenter, placebo-controlled study (Fig. 1). The day before surgery, eligible patients were included and randomly assigned in a 1:1 ratio to receive a continuous infusion of L-bupivacaine (Chirocaïne®, Abbott, Rungis, France) or matching placebo (saline) via a multiperforated catheter. The randomization list was computer-generated, balanced by blocks of variable and undisclosed size, and stratified by the center and by the baseline high or low risk of postoperative pneumonia. A patient was considered at high risk of pneumonia if he had two or more of the following factors: ≥ 70 years old, previous cardiac surgery, chronic obstructive pulmonary disease with forced expiratory volume over 1 s (FEV-1) ≤ 50% and/or a ratio of FEV-1/forced vital capacity (FVC) ≤ 70%, cumulative smoking > 20 cigarettes day^{-1} for at least 20 years, renal dysfunction defined by an estimated preoperative creatinine clearance < 30 mL min^{-1} (Cockcroft–Gault equation), diabetes mellitus requiring insulin therapy, and obesity (body mass index ≥ 30 kg m^{-2}) or cachexia (body mass index < 15 kg m^{-2}) [19–21].

Allocation concealment was achieved using a centralized, secure, interactive, web-response system accessible from each study center (Cleanweb®, Telemedecine Technologies S.A.S., Boulogne-Billancourt, France).

Intervention

L-Bupivacaine and placebo were prepared by an independent pharmacist. Both patient and medical team involved in the study were blinded to the allocated treatment.

A standardized protocol of antibiotic prophylaxis was performed, as recommended by national guidelines. Anesthesia induction and maintenance were performed with propofol and sufentanil in a target controlled infusion adapted to a bispectral index monitoring system (BIS®, Medtronic, MI, USA); the index was maintained at 40–60.

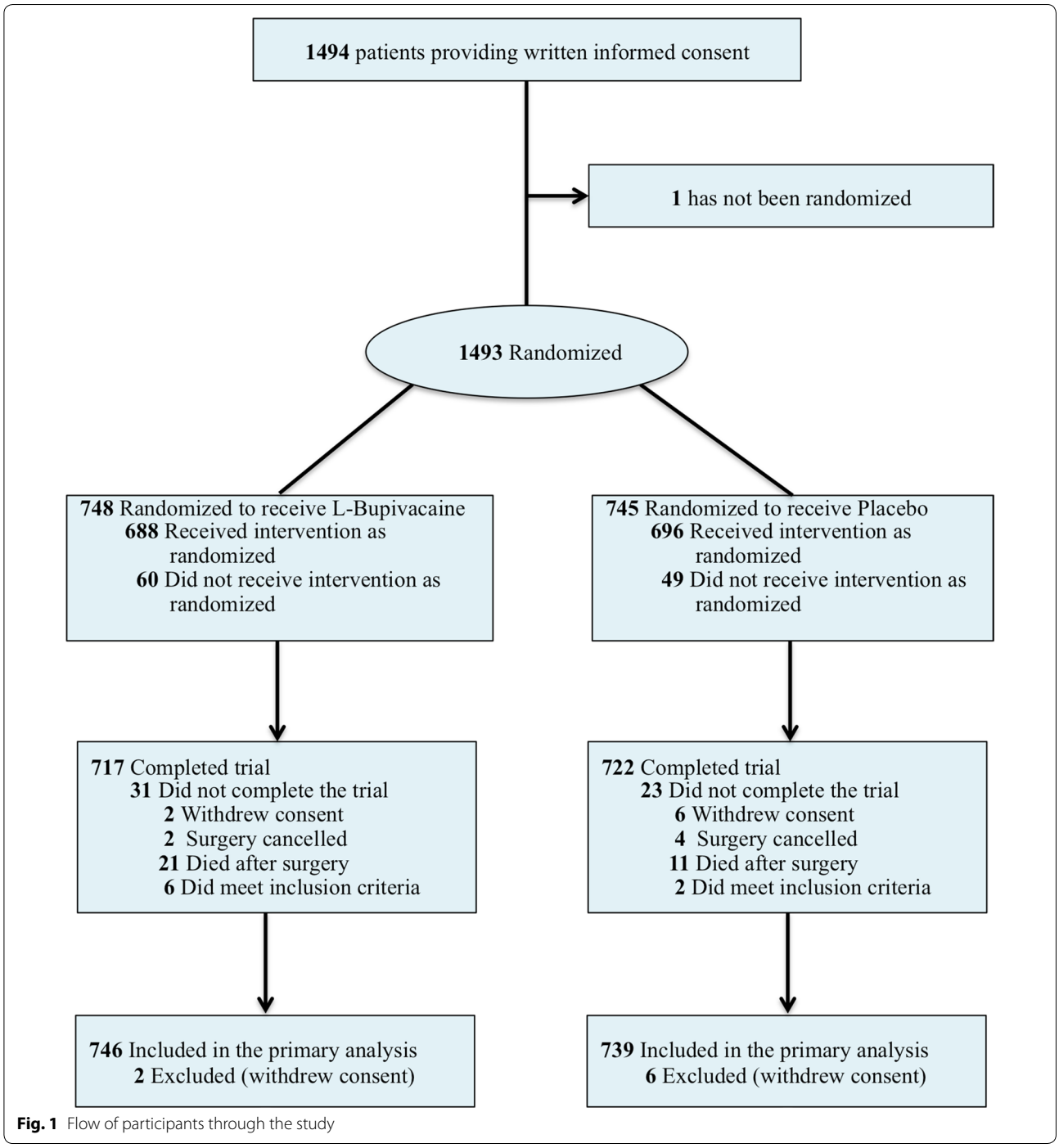

Fig. 1 Flow of participants through the study

After sternal repair and before skin closure, a multiperforated wound catheter (Painfusor®, Baxter, Maurepas, France) was positioned by the surgeon just above the sternal bone and below the adjacent sternal soft tissues in each patient. Depending on the study group, a 10-ml bolus of L-bupivacaine (50 mg) or saline was administered through the catheter (day 0). Then, a continuous infusion (10 ml h^{-1}) of L-bupivacaine (12.5 mg h^{-1}) or saline was started for 48 h using a specific elastomeric pump (Varicon®, Wym France, Paris, France). As recommended in the fast-track cardiac anesthesia strategy, the tracheal extubation was ideally performed within 6 h after the end of skin closure. Initial intravenous morphine sulfate titration was started until the numerical rating scale (NRS) was ≤ 3. Then, morphine was administrated with a patient-controlled analgesia device (PCA, Injectomat Master PCA®, Fresenius Kabi, Sèvres, France). Total cumulative consumption of morphine, including initial intravenous titration, was recorded for each patient during the first 48 h. Both FEV-1 and NRS were assessed at rest and after mobilization during standardized daily physiotherapy sessions during the first 48 h. Between physiotherapy sessions, an incentive spirometer (Respiflo®, Tyco Kendall Healthcare, Elancourt, France) was made available to the patient. A systematic non-invasive ventilation session was performed for at least 1 h per day in ICU. None of our patients was treated with thoracic epidural analgesia. The ICU discharge decision was left to the discretion of the physicians in charge.

Outcomes

The primary end point was the incidence of pneumonia during the study period, i.e., until hospital discharge or 30 days. If a patient had multiple episodes of pneumonia, only the first one was taken into account. The International Sepsis Forum Definition of Infection in the ICU Consensus Conference was used for the diagnosis of infection [22–24]. The retrospective diagnosis of infection was determined independently by three experts, following analysis of the complete medical file [25]. Experts were blinded with respect to patient allocation. The agreement between the three experts was calculated using Fleiss' kappa score.

The secondary end points, assessed during the study period, were ICU-free days defined as the number of days alive until ICU discharge (quoted as 0 if death occurred), hospital length of stay, renal replacement rate, renal replacement therapy-free days, mechanical ventilation-free days, tracheal reintubation, total morphine sulfate consumption, NRS at rest and after mobilization, FEV-1 at rest and after mobilization, septic shock, antibiotic-free days, stroke, and major adverse cardiovascular events (MACCE, defined as the occurrence of stroke and cardiac damage). Myocardial damage was reflected by the highest troponin value measured until the first 24 h. Laboratory explorations were not centralized. All-cause mortality was assessed until 30 days.

The drug safety was assessed during the study period by recording the incidence of seizures, high-degree atrioventricular blocks, ventricular tachycardia or ventricular fibrillation requiring cardioversion, and cardiac arrest. In the specific case of mediastinitis, because it may occur beyond day 30, we performed an additional post hoc analysis until 3 months after surgery by the three experts involved in the retrospective diagnosis of infectious events [24].

Sample size

The sample size estimation was based on an assumed event rate of 18% in the placebo group (median value of the incidence of pneumonia estimated at the different cardiac surgery centers involved, prior to the study). To demonstrate a decrease in the incidence of pneumonia by 30% in the intervention group, with an alpha risk of 0.05 and a beta risk of 0.20, we calculated that 734 patients per group had to be included [26]. To account for potential patient loss on follow-up, we chose to include 750 patients per group, i.e., a total of 1500 patients.

Statistical analysis

An intention-to-treat analysis was performed on all randomized patients, except those who withdrew their consent. In addition, a per-protocol post hoc analysis was performed excluding patients in each group who did not receive the intervention planned by the randomization.

For primary outcome analysis, a generalized linear model (binomial family and identity link function) with adjusted stratification factors (center and baseline risk of pneumonia) was performed to estimate the risk difference of pneumonia between the two groups and its 95% confidence interval (95% CI). In addition, a predefined subgroup analysis was also performed according to the baseline risk of pneumonia, using the same model but including an interaction term between this characteristic and the treatment group.

To handle missing outcome values, three analytical methods were used: a "complete-case" analysis [27], a "worst-best-case" analysis (for which it is assumed that all participants with missing outcome in the L-bupivacaine group have had postoperative pneumonia; and all participants with missing outcome in the placebo group have had no postoperative pneumonia) [27], and a "multiple imputation" analysis. Briefly, multiple imputations

were performed using ten imputed data sets, and results from each imputed data set were pooled using Rubin's rules [28]. The multiple imputation procedure was fully described in supplementary materials. Only the worst-best-case analysis and the multiple imputation analysis include all randomized patients without consent withdrawn, and could be considered as intention-to-treat analyses.

Incidence of pneumonia over time was depicted as a cumulative incidence curve for each group. Death without pneumonia was taken into account as a competing risk, and a Gray's test was used for group comparison.

For secondary end point analysis, quantitative variables were expressed as mean (SD) or median (IQR) in non-normally distributed variables. Comparisons between the two groups were performed using the Student's *t* test or Wilcoxon rank sum test as appropriate. Mean difference between the two groups with 95% CI was reported for normally distributed variables. Qualitative variables were expressed as number (percentage). Comparisons between two groups were performed using the χ^2 Pearson test or the Fisher test when appropriate. Absolute risk difference (with 95% CI) was also reported.

All *P* values were two-tailed, and a $P<0.05$ was considered significant. Sample size calculation and statistical analyses were performed by independent statisticians (AL, DH) using the SAS version 9.4 (SAS Institute, Cary, N.C.).

Results

The randomization and the follow-up of the patients are shown in Fig. 1. A total of 1494 were eligible and 1493 were randomized from March 2012 until November 2014 and followed during 30 days (last follow-up December 26, 2014). The last seven patients were not included for funding reasons.

A total of 1439 patients completed the trial (Fig. 1) and 1384 received interventions as randomized. Overall, 60 (8.0%) patients in the L-bupivacaine group and 49 (6.6%) in the placebo group did not receive the treatment. In addition, 2 (0.3%) patients in the L-bupivacaine group and 6 (0.8%) in the placebo group withdrew consent. Therefore, 746 (99.7%) patients in the L-bupivacaine group and 739 (99.2%) in the placebo group were analyzed on an intention-to-treat 49 (6.6). The L-bupivacaine and the placebo groups were well balanced as shown in the baseline characteristics (Table 1). The surgical procedures are described in Table 2.

Overall, the number of missing values for the primary outcome was 10 (1.3%) in the L-bupivacaine group and 6 (0.8%) in placebo group. In the complete-case analysis, postoperative pneumonia occurred in 36/736 (4.9%) patients in the L-bupivacaine group and in 42/733 (5.7%) patients in the placebo group during the study period (absolute risk difference taking into account a center effect and the baseline risk of pneumonia effect, − 1.3% [95% CI − 3.4 to 0.8], $P=0.22$). The worst-best-case analysis and the multiple imputation analysis provided similar conclusions. Most cases of pneumonia occurred during the first 10 days (Fig. 2). Agreement between experts was good as shown by Fleiss' kappa value measured at 0.80 [95% CI 0.77–0.82]. In per-protocol-analysis, 688 (95.9%) patients in the L-bupivacaine group and 695 (96.3%) in the placebo group were analyzed. The primary end point was not significantly different ($P=0.84$).

In the secondary end point analyses, total consumption of morphine during the first 48 h was slightly reduced in the L-bupivacaine group in comparison with the placebo group, respectively 24 (11–43) and 27 (13−48) mg ($P=0.01$) (Table 3). At rest as well as after mobilization, the quality of analgesia was not significantly different between groups as shown by NRS (Table 3). At rest as well as after mobilization, pulmonary capacity was not significantly different between groups as shown by FEV-1 (Table 3). In addition, the rate of additional surgical incision associated with the sternotomy was not different between groups ($P=0.76$) (Table 2).

ICU-free days, hospital length of stay, renal replacement rate, renal replacement therapy-free days, mechanical ventilation-free days, tracheal reintubation, antibiotic-free days, septic shock, stroke, MACCE, and all-cause mortality until 30 days were not significantly different between groups in the intention-to-treat analysis (Table 3) or per-protocol analysis (eTable 1).

The incidence of serious adverse events was not different between groups in the intention-to-treat analysis (Table 3) or per-protocol analysis (eTable 1).

In the subgroup of patients at high risk of pneumonia, L-bupivacaine significantly decreased the incidence of pneumonia in comparison with the placebo group in the complete-case analysis: 9/233 (3.9%) versus 20/230 (8.7%) (absolute risk difference, − 5.6% [95% CI − 10.0; − 1.2]; $P=0.01$) (Fig. 3a). The multiple imputation analysis (eFig. 1) and the worst-best-case analysis (eFig. 2) showed a similar pattern, but the difference did not reach significance among high-risk patients in the worst-best-case analysis. There was no difference in terms of total morphine consumption and NRS during the first 48 h. Nevertheless, FEV-1 variations after mobilization were significantly improved by L-bupivacaine (eTable 2). Lengths of stay in ICU and in hospital, ventilator-free days, tracheal reintubation, renal replacement-free days, antibiotic-free days (eTable 2), and all-cause mortality until 30 days (Fig. 3b) were not different between groups.

Table 1 Baseline patient characteristics

	L-Bupivacaine ($n=746$)	Placebo ($n=739$)
Age, mean (SD), year	67 (13) [0]	66 (13) [0]
Male sex	526 (71) [0]	542 (73) [0]
Body mass index, mean (SD), kg m^{-2}	27 (4) [0]	27 (4) [0]
ASA class[a]	[0]	[0]
1–2	175 (23)	188 (25)
3	554 (74)	540 (73)
4	17 (2)	11 (1)
Logistic EuroSCORE,[b] median (IQR), %	3.3 (1.8–6.1) [209]	4.00 (2.0–6.0) [201]
LVEF, median (IQR), %	60 (55–67) [51]	60 (55–67) [53]
Diabetes mellitus	145 (19) [0]	161 (22) [0]
Type I	10 (7)	9 (6)
Type II	135 (93)	152 (95)
Hypertension	495 (66) [0]	473 (64) [0]
Ischemic cardiomyopathy	322 (43) [0]	351 (48) [0]
Creatinine clearance, median (IQR), mL min^{-1}	80 (62–104) [0]	83 (62–105) [0]
Patients on long-term dialysis	8 (1) [0]	7 (1) [0]
Dyslipidemia	460 (62) [0]	477 (65) [0]
High risk status of postoperative pneumonia	237 (32) [0]	232 (32) [0]
Age > 70 years old	324 (43)	298 (40)
Previous cardiac surgery	48 (6)	50 (7)
Severe chronic obstructive pulmonary disease	128 (17)	129 (17)
Smoker ≥ 20 pack-years	144 (19)	153 (21)
Body mass index < 15 or > 30 kg m^{-2}	150 (20)	153 (20)
Creatinine clearance < 30 mL min^{-1}	24 (3)	15 (2)
Type II diabetes requiring insulin	32 (4)	40 (5)
Preoperative medication	[0]	[0]
Beta-blockers	405 (54)	375 (51)
Statins	437 (59)	442 (60)
Anticoagulant therapy (INR > 1.5)	5 (1)	8 (1)
Antiplatelet therapy		
Aspirin	396 (53)	416 (56)
Clopidogrel	92 (12)	88 (12)
Prasugrel	3 (0.4)	5 (0.7)
Corticosteroids	32 (4)	18 (2)

Values are expressed as number (percentage), unless otherwise indicated, and followed by [missing data]

SD standard deviation, *ASA* American Society of Anesthesiology, *IQR* interquartile range, *INR* international normalized ratio, *LVEF* left ventricular ejection fraction

[a] ASA class 1, normal healthy patient; class 2, patient with mild systemic disease; class 3, patient with severe systemic disease; class 4, patient with severe systemic disease that is a constant threat to life; and class 5, moribund patient who is not expected to survive without the operation

[b] Logistic Euroscore is a risk model that provides the risk of death after cardiac surgery

Discussion

In this randomized placebo-controlled trial, L-bupivacaine continuous wound infusion for the first 48 h after planned cardiac surgery with sternotomy and CPB did not significantly decrease the incidence of pneumonia during the study period in comparison with placebo and contributes only very slightly to better analgesia. In a subgroup of high-risk patients, L-bupivacaine may decrease the incidence of pneumonia.

After cardiac surgery, pulmonary dysfunction frequently leads to a decrease in pulmonary capacity associated with atelectasis and ventilatory disorders [1–3] in which postoperative pain plays an important role [5, 7–9]. The objective of a multimodal approach including the local anesthetic wound infusion is to improve analgesia [10] and then to improve chest movement, coughing, deep breathing, mobilization, and active chest physiotherapy [9], to decrease opioid consumption

Table 2 Surgical procedures

	L-Bupivacaine ($n=746$) [missing data = 11]	Placebo ($n=739$) [missing data = 8]
CABG	334 (45)	342 (47)
Bilateral internal thoracic artery harvesting	208 (60)	218 (64)
Left internal thoracic artery harvesting only	120 (36)	112 (33)
Other surgical incision associated with the sternotomy		
Saphenous graft	99 (13)	102 (14)
Radial artery graft	1 (0)	0
Carotid endarterectomy	7 (1)	8 (1)
Aortic valve replacement	320 (44)	298 (41)
Mitral valve repair	70 (10)	68 (9)
Mitral valve replacement	48 (7)	49 (7)
Tricuspid valve repair	31 (4)	31 (4)
Ascending aortic surgery	77 (10)	78 (11)
Other procedures	13 (2)	17 (2)
Complex cardiac surgery	153 (21)	148 (20)
CPB time, median (IQR), min	77 (62–103)	77 (61–103)
Aortic cross-clamp time, median (IQR), min	58 (45–78)	59 (45–77)
Total dose of sufentanil, median (IQR), µg	138 (112–165)	136 (110–165)
Total ventilation time, median (IQR), min	600 (480–780)	600 (480–816)

Values are expressed as number (percentage) unless otherwise indicated

CABG coronary artery bypass graft, *CPB* cardiopulmonary bypass, *IQR* interquartile range

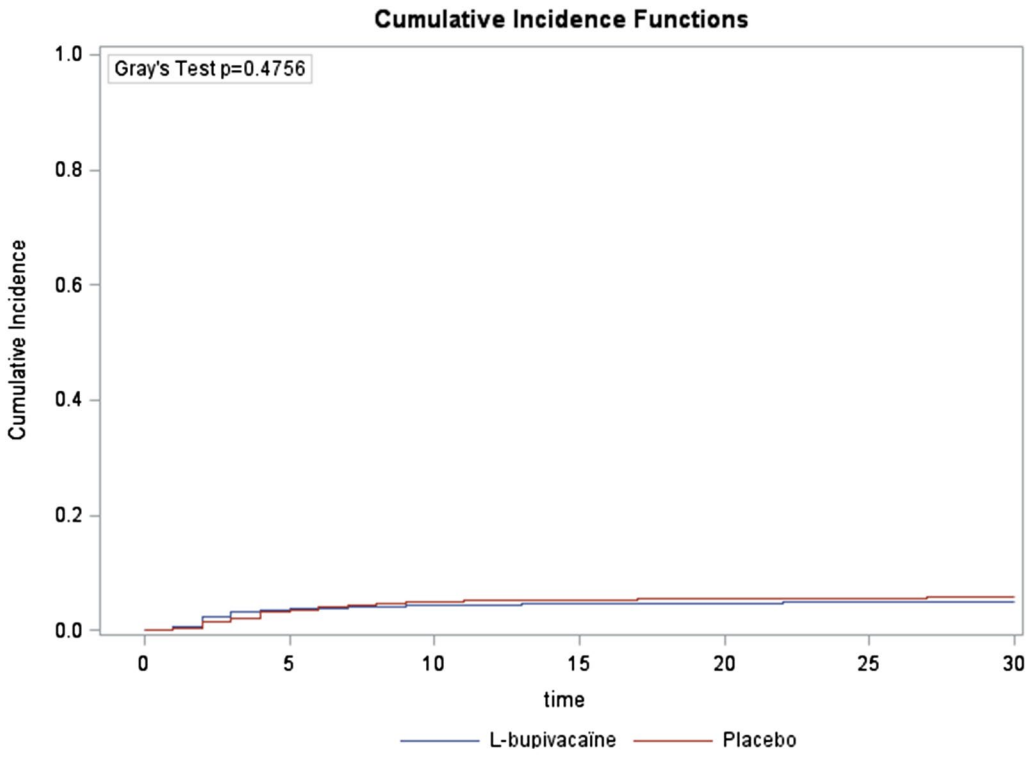

Fig. 2 Comparison of the cumulative incidence of postoperative pneumonia over time between the L-bupivacaine group and the placebo group during the first 30 postoperative days

Table 3 Secondary end points during the study period in analysis population (until hospital discharge or 30 days) (complete-case analysis)

	L-Bupivacaine ($n=746$)	Placebo ($n=739$)	Mean difference, % [95%]	*P* value
Mortality				
All-cause mortality in the first 30 days	21 (3) [7]	11 (2) [6]	1.3 [− 0.2; 2.8]	0.15
In-hospital death	20 (3) [7]	11 (2) [6]	1.2 [− 0.3; 2.7]	0.16
Length of stay, and treatment outcomes during study period				
Length of hospital stay, median (IQR), day	10 (8–14) [10]	10 (8–14) [6]		0.08[$]
Length of ICU stay, median (IQR), day	2 (1–4) [10]	2 (1–5) [6]		0.59[$]
ICU-free days, median (IQR), day	28 (25–29) [7]	28 (25–29) [6]		0.88[$]
Tracheal reintubation	68 (9) [10]	54 (7) [6]	1.9 [− 1; 4.7]	0.07
Septic shock	2 (0.3) [10]	2 (0.3) [6]	− 0.0 [− 0.5; 0.5]	0.99[$]
Ventilator-free days, median (IQR), day	30 (29–30) [7]	30 (29–30) [6]		0.21
De novo renal replacement therapy	25 (3) [10]	27 (4) [6]	− 0.3 [− 2.2; 1.6]	0.85
Renal replacement therapy-free days, median (IQR), day	30 (30–30) [7]	30 (30–30) [6]		0.55[$]
Antibiotics ≥ 1 day	140 (19) [10]	160 (21) [6]	− 2.8 [− 6.9; 1.3]	0.24
Antibiotic-free days, median (IQR), day	30 (30–30) [10]	30 (30–30) [6]		0.44[$]
MACCE	29 (4) [0]	29 (4) [0]	− 0.0 [− 2.0; 1.9]	0.92
Stroke	2 (0.3) [10]	5 (0.7) [6]	− 0.4 [− 1.1; 0.3]	0.28[$]
Postoperative pain outcomes				
Total morphine dose during the first 48 h, median (IQR), mg	24 (11–43) [27]	27 (13–48) [25]		0.01[$]
NRS at day 1, at rest, mean (SD), cm	34 (22) [152]	35 (23) [139]	− 1.4 [− 3.9; 1.6]	0.31
NRS variations at day 1 after mobilization, mean (SD), cm	4 (15) [154]	4 (14) [147]	− 0.8 [− 2.4; 0.8]	0.35
NRS at day 2, at rest, mean (SD), cm	29 (23) [202]	31 (23) [180]	− 1.4 [− 4.1; 1.3]	0.35
NRS variations at day 2 after mobilization, mean (SD), cm	1 (12) [211]	1 (13) [192]	0.3 [− 1.2; 1.8]	0.66
FEV-1 at day 1, at rest, mean (SD), L min^{-2}	173 (64) [154]	167 (67) [145]	6.0 [− 1.5; 13.4]	0.09
FEV-1 variations at day 1 after mobilization, mean (SD), L min^{-2}	23 (40) [155]	20 (36) [154]	3.5 [− 0.8; 7.8]	0.07
FEV-1 at day 2, at rest, mean (SD), L min^{-2}	173 (66) [205]	173 (69) [187]	0.3 [− 7.7; 8.3]	0.89
FEV-1 variations at day 2 after mobilization, mean (SD), L min^{-2}	16 (31) [210]	15 (27) [196]	1.5 [− 2.0; 5.0]	0.37
Safety outcomes				
Mediastinitis in the first 30 days	27(4) [10]	29 (4) [10]	− 0.3 [− 2.2; 1.6]	0.41
Mediastinitis in the first 3 months	28 (4) [10]	31 (4) [6]	− 0.4 [− 2.4; 1.6]	0.48
Seizures during study period	3 (0.4) [0]	4 (0.1) [0]	0.3 [− 0.2; 0.8]	0.62[$]
High-degree atrioventricular block during study period	11 (2) [0]	9 (1) [0]	0.3 [− 0.9; 1.4]	0.98
Major ventricular arrhythmia treated by cardioversion during study period	12 (2) [0]	10 (1) [0]	0.3 [− 1.0; 1.5]	0.68[$]
Cardiac arrest during study period	8 (1) [0]	11 (1) [0]	− 0.4 [− 1.6; 0.7]	0.53

Values are expressed as number (percentage), unless otherwise indicated, and followed by [missing data]

SD standard deviation, *IQR* interquartile range, *ICU* intensive care unit, *MACCE* major adverse cardiac and cardiovascular events, *NRS* numerical rating scale, *FEV-1* forced expiratory volume in 1 s

[$] All statistical tests were adjusted on stratification factors (center and baseline risk of pneumonia) except (indicated with[$]) in case of deviation from the normality assumption or convergence issues with the multivariate model

and its related side effects, and then to improve patient outcomes [11]. The use of thoracic epidural analgesia, which has been shown to be an efficient analgesic therapy in thoracic surgery, is still a matter of debate in cardiac surgery because of the increased risk of perimedullary hematoma associated with the high concentration of anticoagulation therapy required for CPB [29, 30]. In parallel, small studies suggested the safety of local anesthetic continuous wound infusion in reducing postoperative pain [14, 15]. A meta-analysis of 42 heterogeneous studies involving 2141 patients undergoing various types of surgery revealed the superiority of analgesia combining morphine and local anesthetic wound infusion compared with morphine alone [31]. This results in a 40% decrease in overall morphine consumption. In cardiac surgery, despite the small size of

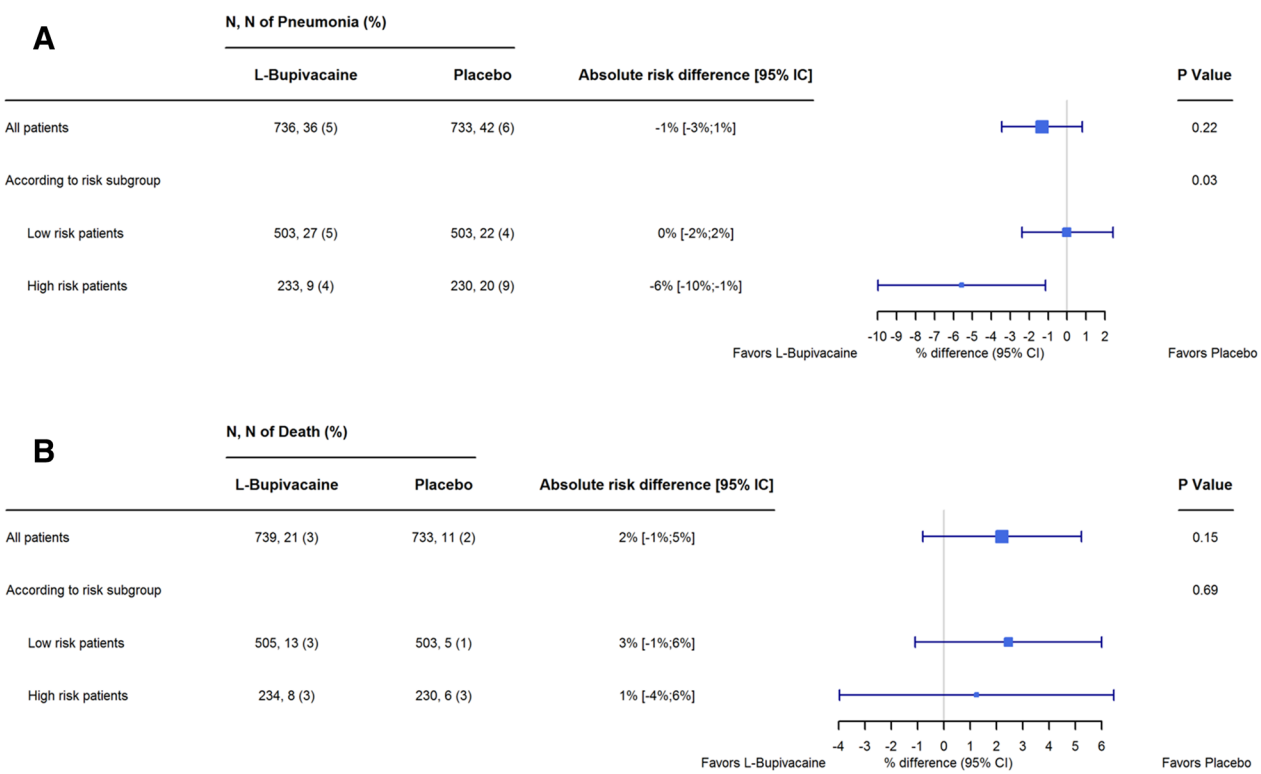

Fig. 3 Forest plot of the absolute risk difference in the primary end point (**a**) and mortality (**b**) according to predefined subgroups of preoperative high- and low-risk status for postoperative pneumonia, in complete-case analysis. Tests are adjusted on center and preoperative risk of pneumonia effect. The *P* value "According to risk subgroup" corresponds to the interaction test. 95% IC, 95% confidence interval; N, number

the few studies carried out, the results suggested a significant beneficial analgesic effect of local anesthetic wound infusion [1, 14–16]. In a recent small trial performed in a single center, Eljezi et al. observed a better effect of respiratory physiotherapy, despite the lack of enhancement of spirometric variables, in parallel with a significant decrease in pain, both at rest and during chest mobilization [1]. These results were associated with a significant decrease in the incidence of all-cause pulmonary complications, without being able to conclude on the incidence of pneumonia. In the current study, with a much larger sample size and a double-blind intervention, the incidence of pneumonia during the study period was similar between groups. Despite a slight decrease in morphine consumption during the first 48 h, pain score (NRS) and lung capacity (FEV-1) were not improved by L-bupivacaine. The secondary end points were not improved. Overall, when a large double-blind trial is provided, the slight beneficial analgesic effect of L-bupivacaine is not enough to improve postoperative respiratory function and the incidence of pneumonia.

In high-risk patients, in complete-case analysis as well as in multiple imputation analysis, our results suggest that L-bupivacaine may decrease the incidence of pneumonia. The potential beneficial effect of L-bupivacaine may be explained by better chest mobilization and improved lung capacity as shown by the increase of FEV-1 up to 10% after mobilization in the L-bupivacaine group. The fact that NRS and total morphine consumption did not improve in this subgroup suggests the highly subjective and variable nature of these parameters from one individual to another. Regardless, improved chest mobilization indirectly reflects improved analgesia. Of course, further randomized study focused on high-risk patients should be performed to confirm this hypothesis because, on the one hand, this is a subgroup statistical analysis and, on the other hand, two of the statistical analyses performed, complete-case and multiple imputation, concluded a significant difference between L-bupivacaine and placebo groups but the worst-best-case analysis, the most unfavorable regarding the experimental group, did not.

Overall, despite the implantation of the catheter in the sternal wound, we did not observe any difference in mediastinitis rate between groups. The relatively high rate of mediastinitis in the current study (4%) is consistent with the high proportion of CABG performed with

bi-mammary artery grafts and the high proportion of diabetic and obese patients [32, 33].

This study has several limitations. The first, and obviously the most important, is the overestimation of the expected incidence of pneumonia. The observed incidence was very much lower (5.4%) than hypothesized for the sample size calculation (18%). Unfortunately, our hypothesis was based on the literature data at the time we wrote the study protocol in 2010, which was quite wide-ranging (3–30%) [1–4]. The high heterogeneity in the diagnostic criteria of pneumonia used in these different studies may contribute to this large range. In addition, because pneumonia is a difficult diagnosis and overestimated in daily practice, its incidence measured for the sample size calculation in our five centers was also probably overestimated. To support this hypothesis, during this study, the diagnosis of pneumonia by the physicians in charge was twofold increased in comparison to the retrospective diagnosis made by the three experts. This overestimation by the physician may also explain the lack of difference of total antibiotic consumption and antibiotic-free days in the high-risk subgroup, although there is a trend. Nevertheless, the lack of consistent beneficial effect in the whole population raises the question of the futility of this treatment outside perhaps high-risk patients. A second limitation is the potential bias of interpretation which may have resulted from a high rate of very late onset pneumonia (>10 days), long after the peak of postoperative sternal pain known to occur during the first 48 h, and thus long after the potential beneficial effect of continuous infusion of L-bupivacaine. However, we observed that most pneumonia occurred during the first 10 days. Third, 7.3% of patients did not receive the intervention as randomized, which may also limit the power of the study. However, the per-protocol analysis confirmed the results of the intention-to-treat analysis. Lastly, the catheter may be in an inadequate sternal position and/or the dose of L-bupivacaine administered may be insufficient. Nevertheless, beneficial effect of local anesthetic was found with sternal wound infusion, at lower rate of infusion [14–16]. Nevertheless, those monocentric studies investigated samples size of less than 30 patients in total. This underlines the importance of conducting large double-blind multicenter trials, especially when they focus on analgesia.

Conclusion

In patients undergoing cardiac surgery with sternotomy and CPB, local anesthetic continuous wound infusion failed to decrease the incidence of postoperative pneumonia. These findings do not support the routine use of continuous wound infusion of L-bupivacaine in this indication. Nevertheless, further studies should investigate its potential beneficial effect in high-risk patients.

Electronic supplementary material

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Author contributions

Drs JA and DH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: AB, BC, AO, DL, J-LF, DH, BR, JA. Acquisition of data: all authors. Analysis, or interpretation of data: AB, BR, AL, DH, JA. Drafting of the manuscript: AB, BR, JA. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: AL, DH. Obtained funding: JA. Administrative, technical, or material support: DH. Supervision: JA, DH.

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Compliance with ethical standards

Conflicts of interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. No disclosure was reported.

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Baxter, Abbott France, and Wym France Orion Pharma had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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