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ORIGINAL ARTICLE

Bilateral sternal infusion of ropivacaine and length of stay in ICU after cardiac surgery with increased respiratory risk

A randomised controlled trial

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BACKGROUND The continuous bilateral infusion of a local anaesthetic solution around the sternotomy wound (bilateral sternal) is an innovative technique for reducing pain after sternotomy.

OBJECTIVE To assess the effects of the technique on the need for intensive care in cardiac patients at increased risk of respiratory complications.

DESIGN Randomised, observer-blind controlled trial.

SETTING Single centre, French University Hospital.

PATIENTS In total, 120 adults scheduled for open-heart surgery, with one of the following conditions: age more than 75 years, BMI >30 kg m^{-2}, chronic obstructive pulmonary disease, active smoking habit.

INTERVENTION Either a bilateral sternal infusion of 0.2% ropivacaine (3 ml h^{-1} through each catheter; 'intervention' group), or standardised care only ('control' group). Analgesia was provided with paracetamol and self-administered intravenous morphine.

MAIN OUTCOME MEASURES The length of time to readiness for discharge from ICU, blindly assessed by a committee of experts.

RESULTS No effect was found between groups for the primary outcome ($P = 0.680$, intention to treat); the median values were 42.4 and 37.7 h, respectively for the control and intervention groups ($P = 0.873$). Similar nonsignificant trends were noted for other postoperative delays. Significant effects favouring the intervention were noted for dynamic pain, patient satisfaction, occurrence of nausea and vomiting, occurrence of delirium or mental confusion and occurrence of pulmonary complications. In 12 patients, although no symptoms actually occurred, the total ropivacaine plasma level exceeded the lowest value for which neurological symptoms have been observed in healthy volunteers.

CONCLUSION Because of a small size effect, and despite significant analgesic effects, this strategy failed to reduce the time spent in ICU.

TRIAL REGISTRATION EudraCT (N°: 2012-005225-69); ClinicalTrials.gov (NCT01828788).

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Introduction

Pain after open cardiac surgery, primarily located at the sternotomy incision, is often of severe intensity, and is aggravated by coughing, deep breathing, moving or turning in bed and mobilisation.[1–4] A relationship between pain intensity and impairment of pulmonary function after sternotomy has already been shown,[5,6] generating

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the hypothesis that insufficient pain relief favours pulmonary complications.[7–9] The latter are indeed a frequent cause of morbidity after cardiac surgery,[10–12] especially when risk factors, such as older age, obesity, chronic obstructive pulmonary disease (COPD) and smoking history apply.[7] Such complications may have serious consequences, as they prolong hospital stay and may increase costs and even mortality.[11,13]

To stop this vicious cycle, strategies aimed at reducing pain, especially its 'dynamic' aspect during movement, and active encouragement of early physiotherapy and mobilisation, would probably reduce the risk of postoperative complications.[14–16] However, such strategies need effective analgesia such as that provided by thoracic epidural analgesia (TEA), which has been shown to reduce the rate of pulmonary infection in cardiac surgery.[17] A continuous bilateral sternal (BLS) infusion of a local anaesthetic through multihole catheters to provide a nociceptive block of the anterior branches of intercostal nerves at the lateral margins of the sternum,[18] is an emerging alternative to TEA. We recently tested it against placebo in a double-blind design in nonselected patients undergoing open cardiac surgery and found it to be effective in the reduction of dynamic pain (the primary outcome in that study) and to facilitate some aspects of rehabilitation.[19] We also hypothesised that the local anaesthetic itself could act positively on pulmonary vascular inflammation and endothelial hyperpermeability.[20] Lastly, the BLS catheter insertion is an easy technique with a short learning curve, and very low rates of failure and complications. We therefore wished to study its potential impact on postoperative morbidity, in a selected sample of patients at risk of postoperative pulmonary complications. The primary outcome we targeted was the length of time to readiness for discharge from the ICU.

Methods

Trial design and participants

This randomised, observer-blind, controlled trial was approved by the relevant research ethics committee (CPP Sud-Est VI, Clermont-Ferrand,) on 16 January 2013 and registered with EudraCT (N°: 2012–005225-69) and on ClinicalTrials.gov (NCT01828788). Inclusion criteria were patients scheduled for open-heart surgery with sternotomy and cardiopulmonary bypass (CPB) for valve replacement or coronary artery bypass grafting, with at least one of the following respiratory risk factors: age more than 75 years; BMI more than 30 kg m^{-2}; COPD defined by the preoperative forced expiratory volume to forced vital capacity ratio (FEV1/FVC), assessed either by a specialist physician or by the team who completed the preoperative assessment, or smoking habit, either active or discontinued within the last 3 months. Exclusion criteria were emergency surgery or heart transplant, aortic dissection, scheduled additional thoracotomy, reoperation, left ventricular ejection fraction less than 40%, mean pulmonary arterial pressure more than 50 mmHg, preoperative cardiac failure or using intra-aortic balloon pump, vital capacity or FEV1 less than 50% of predicted values, renal insufficiency with creatinine clearance less than 30 ml min^{-1}, pregnancy, cognitive impairment or incapacity to sign the informed consent or to use patient-controlled analgesia (PCA), chronic use of opioids or drug addiction, and known allergy to any of the study drugs. Patients received a detailed study explanation at preoperative consultation, and the day before surgery, after giving their signed consent, they were instructed how to rate their pain from 0 (no pain) to 10 (maximum pain imaginable) on a numerical rating scale and in the use of the PCA.

Interventions

The evening before surgery and 1 h before anaesthesia, the patients received 1 mg kg^{-1} of oral hydroxyzine. On arrival in the operating theatre, venous access was established with one large peripheral intravenous cannula. A radial artery cannula for direct blood pressure monitoring, five-lead electrocardiography, pulse oximetry and monitoring of bispectral index (BIS) and neuromuscular blockade were set up. General anaesthesia was induced with intravenous (i.v.) propofol 1 to 2 mg kg^{-1}, sufentanil 0.3 μg kg^{-1} and cisatracurium 0.15 mg kg^{-1}. After tracheal intubation, the lungs were mechanically ventilated with oxygen (30 to 100% according to SpO_2) and air at 12 breaths per minute and a 7 ml kg^{-1} tidal volume adjusted to maintain end-tidal carbon dioxide values in the 27 to 32 mmHg range. Positive end-expiratory pressure was not applied. After induction, a four-channel central venous line was inserted into the internal jugular vein, and a catheter was inserted into the bladder for continuous drainage of urine. Patients were given 1.5 g of i.v. cefuroxime and 2 g of i.v. tranexamic acid. Anaesthesia was maintained with sevoflurane before and after CPB and propofol during CPB. The rate of administration was titrated to maintain BIS between 40 and 60. Analgesia was provided with sufentanil 0.5 μg kg^{-1} h^{-1} and muscle relaxation with cisatracurium 0.6 mg kg^{-1} h^{-1} titrated to give a null response in the train of four. At the withdrawal of CPB, cardiovascular performance was improved by measures that included temporary tilt position, intravascular fluid loading, cardiac electrical pacing, vasopressors and inotropic support.

Before the end of surgery all patients were randomised into either the control group, who received a standard postoperative analgesia regimen or the interventional group who received the same standard regimen and analgesia with BLS infusion of ropivacaine.

The propofol infusion was maintained during transport from theatre to the ICU and until tracheal extubation. T0 was the time of the patient's arrival in the ICU. Routine intensive care monitoring, chest radiography

and electrocardiography were performed on all patients. Standard laboratory tests were done at T0, then daily and at the physician's request; plasma troponin (cTnI) was measured at T0, T0+6 h and T0+12 h as a minimum. Heparin 50 IU kg^{-1} day^{-1} was started at the sixth hour after surgery (except special cases), and was then increased as indicated clinically; aspirin 75 to 250 mg day^{-1} was also given. The propofol infusion was discontinued when the vital signs were considered to be stable. Extubation was performed once the patient had adequate haemostasis, was able to respond to simple commands and could breathe spontaneously. Patients were then placed in a 30° sitting position.

Postoperative analgesia was standardised for the two groups and included 1 g of i.v. paracetamol every 6 h and i.v. morphine chlorhydrate, when requested by the patient in the ICU (2 mg i.v. boluses until pain score $\leq$3/10), then delivered via a PCA device.

In the intervention group, two multihole catheters with a 19 cm diffusion area (ON-Q SilverSoaker: I-Flow Corporation, Lake Forest, CA, USA) were inserted by the surgeon after sternotomy closure. They were inserted with the help of a 17 Gauge × 8 inches tunneler (ON-Q Tunneler Sheath: I-Flow Corporation, Lake Forest, CA, USA), inserted lateral to the xiphoid at the subcostal margin and directed upwards below the pectoral muscles over the costo-sternal margin parallel to the sternotomy incision. These catheters were connected by a Y-shaped tube to a continuous flow perfusion device (Halyard Health, Irvine, California, USA) to administer the local anaesthetic. A single suture was used to close the introduction point and to secure the catheter. Following insertion of the catheters and a negative aspiration test, the patients received 10 ml of 0.2% ropivacaine (Naropin 2 mg ml^{-1}, AstraZeneca, Rueil-Malmaison, France). After the initial bolus, a continuous infusion of ropivacaine 0.2% was administered at a fixed rate of 6 ml h^{-1} for 48 h. The patients in the control group did not have catheters inserted.

Haemodynamic support, if necessary, included intravenous fluid loading, inotropic support, norepinephrine or urapidil. Vital signs, Glasgow coma scale, level of sedation, urine output, chest tube drainage volume and gastrointestinal function were recorded at T0+4 h, then every 4 h until T0+48 and then every 8 h until 80 h. Patients were transferred to oral therapy if possible after the first postoperative day, with priority given to cardiovascular drugs and to preoperative treatment. Gastrointestinal function was assessed from the first morning after surgery by recording the first event of the following outcomes: flatus, faeces, dietary intake and oral medication intake. Patients were transferred to the surgical ward when none of the following supports were necessary: inotrope or vasopressor treatment, mechanical ventilation, dialysis and there was no life-threatening disturbance of rhythm. Physiotherapy began at T0+24 h if possible, with 15-min sessions once or twice a day and self-managed exercises. The programme included multimodal controlled respiratory exercises (diaphragmatic breathing, inspiratory flow control, forced expiration with open glottis and cough) and active mobilisation (favouring the lower limbs).

Just before the beginning of BLS infusion and at 12, 24, 36 and 48 h afterwards, blood samples for ropivacaine analysis were drawn from those patients receiving the ropivacaine infusion. The total ropivacaine plasma concentration was measured by High Performance Liquid Chromatography (HPLC) after solid-phase extraction. The solid-phase extraction was performed using a Vac-Elut system (Varian Medical Systems Inc., Palo Alto, CA, USA) and C18 100-mg cartridges (Macherey Nagel, Hoerdt, France). Before the solid phase extraction of the sample, 20 µl of a 50 mg l^{-1} aqueous lidocaine solution (used as an internal standard) was added to 980 µl of plasma sample (final lidocaine concentration of 1 mg l^{-1}). One ml of this solution was extracted with a C18 cartridge previously rinsed with 2 ml of methanol and 2 ml of water. After sample extraction, the cartridge was washed with 2 ml of acetonitrile–water (30 : 70 v/v) to eliminate undesirable compounds (but not ropivacaine or lidocaine) and left to dry for 3 min. Purified ropivacaine and lidocaine fixed on the cartridge were then eluted with 1 ml of methanol, and 50 µl of this eluate were injected onto the chromatographic system. The analysis was carried out with a 150 × 4.6 mm^2 intradermal Spherisorb Phenyl 5-µm analytical column (Waters, Saint-Quentin-en-Yvelines, France) fitted on a liquid chromatographic system composed of an AS-2055 Plus autosampler, a PU-2080 Plus pump and a UV-275 ultraviolet detector (Jasco, Lisses, France). The mobile phase was an acetonitrile–potassium phosphate buffer (0.01 M, pH 4.7) 60 : 40 v/v and the flow rate was 1.5 ml min^{-1}. Absorbance was measured at a wavelength of 210 nm. Lidocaine and ropivacaine were obtained from AstraZeneca (Södertälje, S). Six calibration standard solutions were prepared to create the calibration curve: 80 µl of ropivacaine stock solution (respectively 1.875, 3.75, 7.5, 15, 30, 60 mg l^{-1}), and 20 µl of a 50 mg l^{-1} aqueous lidocaine solution used as an internal standard were added to 900 µl human plasma from the blood transfusion centre at Clermont-Ferrand (final concentration from 0.15 to 4.8 mg l^{-1} for ropivacaine, and 1 mg l^{-1} for lidocaine). These calibration plasma solutions were then extracted as described above before analysis of the test solutions. The ultraviolet absorbance measured by the detector at 210 nm was linear for ropivacaine concentrations ($r^2 > 0.9999$). The method has a high level of precision, with intra-day and inter-day variation coefficients of less than 5% and the accuracy is correct (< 7%). The limit of quantification was 0.15 mg l^{-1}. The ropivacaine recovery rate was better than 90%.

Outcomes and sample size calculation

The primary outcome measure was the length of time (h) to readiness for discharge from ICU. The secondary outcomes were the in-ICU and in-hospital length of stay (LOS), readmissions to the ICU, pain scores at rest and on mobilisation, opioid consumption, the time to get out of bed with assistance to sit in a chair, duration of oxygen therapy, time to first dietary intake and oral medication intake, nausea and vomiting score, patient satisfaction, postoperative complications and occurrence of neuropathic pain persisting six months after surgery. The occurrence of a postoperative pulmonary complication was defined according to the Melbourne Group Scale, validated in 2008 [21] and used as an outcome in thoracic surgery,[22] (at least four of the following events: atelectasis or infiltration on chest X-ray, purulent sputum, physician diagnosis of pneumonia/chest infection, temperature >38°C, SpO_2 <90% on air, positive signs on sputum microbiology, white cell count >11.2 units or readmission/prolonged stay in ICU). Renal insufficiency was defined as a serum creatinine level more than 220 mmol l^{-1} or a need for haemodialysis. Other relevant neurological, cardiac and infectious complications were also noted, in accordance with recently published European standards.[23]

Pain was assessed on numerical rating scale at the same frequency as for vital signs, first at rest (sites considered: sternal, back, and leg in the case of saphenous harvesting), then during coughing, just after the patient was placed horizontally for the measurement of central venous pressure, and just after each nursing session, following turning into a lateral position. At T0+80 h, morphine consumption and patient satisfaction on a five-point scale (0: very bad; 1: bad; 2: average; 3: good; 4: very good) were noted. Sedation was assessed with a Ramsay scale. Nausea or vomiting was noted. A procedure for identification and treatment of overdose of local anaesthetic was made available.

Six months after surgery, the patients were telephoned and asked to respond to a standardised questionnaire requesting details of sternal pain, the neuropathic mechanism of which was identified by a validated discriminant tool, the DN4.[24]

The sample size was estimated on the basis of data on the actual LOS in the ICU, taken from our department in a similar cohort over the whole of the year 2011. As this variable followed a skewed asymmetric distribution with outliers (median value = 70 h), we withdrew the cases with a LOS more than 5 days (likely to correspond to a complication, in our experience), resulting in the variable following a Gaussian distribution for the remaining cases (75% of the whole sample), with SD = 32 h. To identify a 24-h difference in the LOS in ICU, with $\alpha = 5\%$ and $1-\beta = 90\%$, the number of patients per group was estimated at 40, or 60 if the 25% of cases with a LOS exceeding 5 days were included.

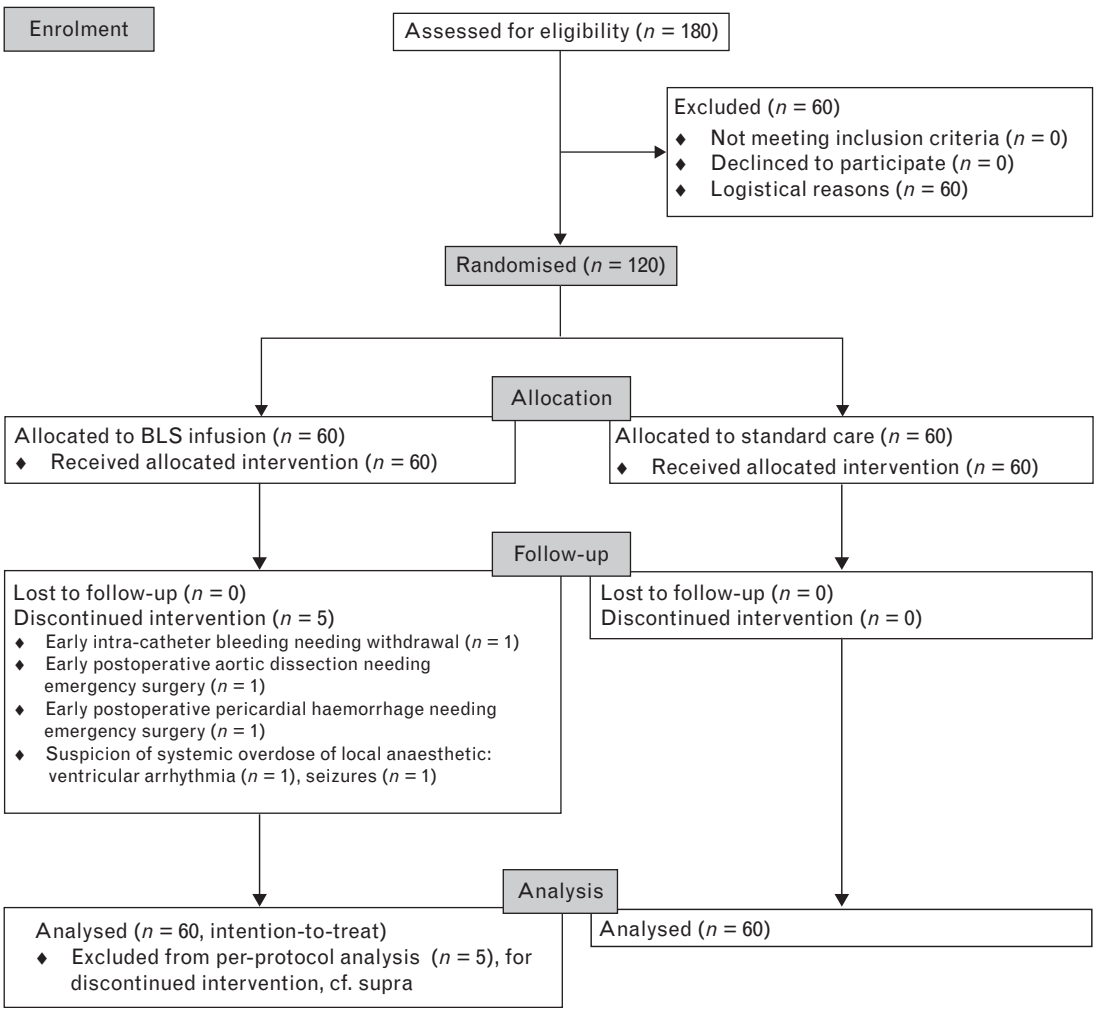
Limitation of potential biases

Patients were randomly assigned prior to the study following a plan with a block size of 4, by an independent research assistant responsible for sealed envelopes containing the allocated treatment and the inclusion number. The length of time to readiness for discharge from ICU was defined for each patient by an independent adjudication committee of two anaesthetists experienced in perioperative care in cardiac surgery (C.D. and P.S.) and a cardiac surgeon (K.A.), according to a predefined checklist, irrespective of the actual delay in discharge after this time. The members of this committee were all blind to the patient's name and the treatment given. The checklist was based on published recommendations.[25] Each case was presented as a standard electronic file (Excel 2003, Microsoft, Redmond, Washington, USA) based on information from the hospital electronic system containing the clinical data from the ICU, as well as the data recorded in the surgical ward on the case report form. If the coefficient of variation (CV, calculated from the three values of the primary outcome obtained for each case) exceeded 30%, before a second assessment was carried out by the committee to replace this value the members met to agree the reason for the discrepancy and the value(s) to be corrected. The aim was to set a new value such that the new CV was below 30%. The three final values were then averaged. The occurrence of postoperative complications was also analysed by a blinded investigator through direct analysis of the patients' hospital data.

Statistical methods

Analyses were performed using Stata 13 (StataCorp, College Station, Texas, USA). The tests were two sided, with $\alpha = 0.05$. The primary outcome was analysed on an intention to treat basis as well as per-protocol received, and secondary outcomes per-protocol only. In case of in-hospital death, the primary outcome was replaced by the longest actual LOS in ICU in the whole sample. Quantitative data were expressed as mean ± SD if normally distributed, otherwise as quartiles. The normality of the distribution was checked with a Shapiro–Wilk test. Comparisons between groups for nonrepeated data were conducted using, for categorical variables, χ^2 or Fisher's exact tests, and for quantitative variables, either Student *t*-test for a normal distribution and homoscedasticity, or Mann-Whitney test otherwise. For comparisons of pain scores between the two groups, the raw data were analysed without replacing the missing data. In addition, at each observation time, composite scores for pain at rest (static) and on mobilisation (dynamic) were generated. Static pain was the average of sternal and dorsal pain at rest; dynamic pain was the average of pain on coughing, after repositioning for measurement of central venous pressure and after turning into a lateral position during nursing care. Missing data were replaced using the formula from a linear regression conducted with the observations containing full data, first within each domain

Fig. 1



CONSORT 2010 flow diagram of the trial.

of pain (static/dynamic), then, in the case of all data being absent for one domain, with information taken from another domain. This approach was chosen to improve the estimation of the effect size for each domain of pain. Repeated longitudinal data were analysed using random effects regression models (group, time points evaluation and their interaction as fixed effects) taking into account between and within patient variability (subject as random effect). The normality of residuals was checked.

Results

Participant flow and recruitment

The trial started on April 2013 and ended on May 2014. The CONSORT flow chart of the trial is shown in Fig. 1. There were two patients for whom systemic overdose of local anaesthetic was suspected but the plasma concentrations of ropivacaine were low and the doses given were nontoxic.

Baseline data

The two groups had similar baseline characteristics (Table 1). The most frequent entry criterion for respiratory risk was obesity (54.8% of the whole sample), followed by age over 75 (33.0%), active smoking habit (27.0%) and COPD (20.0%).

Outcomes and effects

Regardless of the type of analysis, no effect was shown on the primary outcome, the length of time to readiness for discharge from ICU (Table 2). Nevertheless, a general nonsignificant trend of improved recovery is suggested for the BLS group.

Analgesia was also better in the BLS group, mostly for pain on movement (Table 2 and Fig. 2). This analgesic effect decreased with time; the effect on static pain was only apparent for the early observations, whereas it was preserved throughout the duration of the study for

Table 1 Baseline characteristics

	Control ($n = 60$)	BLS ($n = 55$)	*P* value
Preoperative characteristics			
Age (years)	68.4 ± 9.3	67.9 ± 9.8	0.798
Age >75 years	20 (33.3)	18 (32.7)	0.945
Sex: women	9 (15.0)	9 (16.4)	0.841
BMI (kg m^{-2})	29.4 ± 4.4	30.7 ± 4.9	0.123
BMI > 30 kg m^{-2}	29 (48.3)	34 (61.8)	0.147
Previous medical history			
Euroscore 2 (%)	1.62 ± 1.16	1.85 ± 1.25	0.322
Chronic obstructive pulmonary disease	14 (23.3)	9 (16.4)	0.469
Active smoking habit	16 (26.7)	15 (27.3)	0.942
Sleep apnoea syndrome	5 (8.3)	3 (5.7)	0.721
Arterial hypertension	29 (48.3)	29 (54.7)	0.498
Peripheral arterial disease	11 (18.3)	11 (20.8)	0.746
Atrial fibrillation/flutter	8 (13.3)	6 (11.3)	0.783
Pulmonary arterial hypertension	6 (10.0)	8 (15.1)	0.569
Stroke	5 (8.3)	6 (11.3)	0.753
Diabetes	14 (23.3)	17 (32.1)	0.299
Dyslipidaemia	23 (38.3)	22 (41.5)	0.731
Chronic renal insufficiency	3 (5.0)	1 (1.9)	0.621
Thyroid disease	4 (6.7)	4 (7.8)	1.000
Mental disease	7 (11.7)	2 (3.4)	0.170
Summary: no. of entry criteria for respiratory risk[a]			
1	43 (71.7)	34 (61.8)	0.127
2	15 (25.0)	21 (38.2)	
3	2 (3.3)	0 (0.0)	
Surgery and anaesthesia			
Total duration of surgery (min)	237 ± 63	233 ± 72	0.748
Duration of extracorporeal circulation (min)	84 [62.5 to 110.5]	87 [61 to 109]	0.920
Duration of aortic cross clamping (min)	65 [49.5 to 89]	68 [49 to 85]	0.910
Dose of intraoperative sufentanil (μg)	158 [125 to 181]	150 [129 to 180]	0.894
Valve replacement	37 (61.2)	37 (67.3)	0.393
Aortic	33	34	NC
Mitral	4	5	
Tricuspid	3	1	
Ascending aorta	3	5	
Coronary bypass	35 (58.3)	25 (45.5)	0.167
Internal thoracic artery harvesting			
Left	32 (53.3)	25 (45.5)	NC
Right	17 (28.3)	12 (21.8)	
Saphenous harvesting	14 (23.3)	12 (21.8)	
No. of anastomoses (when applicable)			
1	9	4	NC
2	12	5	
3	8	13	
4 to 5	6	3	

Patient characteristics from control and BLS groups. Numerical data are expressed as mean ± SD or median (interquartile range). Categorical data are expressed as number of patients and percentage. BLS, bilateral sternal; NC, not calculated. [a]The criteria were: age >75 years, BMI > 30 kg m^{-2}, active smoking habit, or chronic obstructive pulmonary disease.

dynamic pain. The patients who received the BLS ropivacaine infusion also reported better satisfaction with their care than the control group (Table 2).

In general, there were no differences between groups in the incidences of postoperative complications (Table 3), although there was a lower incidence of pulmonary complications (according to the Melbourne Group Scale), and of delirium and mental confusion in the BLS group, and – for the other outcomes – a general trend for lower risk in the BLS group. The studied treatment had no impact on long-term pain outcomes.

The values for total ropivacaine plasma concentration are shown in Fig. 3. It demonstrates that the treatment had been administered to all the allocated patients. A trend to increased concentrations with time was noted, with a mean slope of 0.052 mg l^{-1} h^{-1}. The safety threshold value of 3.4 mg l^{-1} was exceeded in 12 patients (22.2%), for a total of 22 observations, all but one occurring after T0+12 h. No symptoms of overdose were noted.

Discussion

Main results

Despite significant effects of BLS analgesia with ropivacaine on important postoperative outcomes, such as improved pain relief and patient satisfaction, lower opioid consumption, better participation in respiratory physiotherapy and fewer pulmonary complications, the BLS treatment did not reduce the time to readiness for discharge from ICU. The reason for this lack of effect seems to be because of the small effect size (4 h in the per-protocol analysis). The study had insufficient power to highlight any significant differences.

External validity

To help understand our results, we must first compare them with those of our preliminary pilot study conducted in nonselected patients, in which the BLS infusion provided better analgesia, both at rest and during mobilisation.[19] In our current study, analgesic effects occurred even earlier, probably because of improvements in the technique: by increasing the insertion length from 12.5 to 19 cm to improve the drug diffusion and by increasing the drug doses. Also, in the current trial, the open design could have increased the analgesic effect. Although the previous study reported an improvement of dietary intake, mobilisation and involvement in physiotherapy, these effects were too small to be significant here. However, a lower incidence of pulmonary complications in patients with increased respiratory risk was noted in this study, although such a risk was probably too low to be affected by the BLS analgesia in nonselected patients. We must also point out that, despite a reduction in dynamic pain, the technique did not affect the postoperative spirometric outcomes.[19] We have no grounds for a 'no pain, no gain' theory, as the pain scores in our control group were no lower than those reported in similar control groups, with paracetamol and morphine *ad libitum*.[26,27] To summarise, we suggest that better analgesia – even if it has positive effects on physiotherapy and therefore reduces the risk of pulmonary complications – is not sufficient to reduce the LOS in ICU. Therefore, physiological factors other than pain must be targeted to achieve that end.

Table 2 Postoperative recovery outcomes

	Control ($n = 60$)	BLS ($n = 55$)	*P* value
Length of time to readiness for discharge from ICU (h)			
Intention to treat[a]	42.4 (19.6 to 72.7)	41.4 (24 to 65)	0.680
Per-protocol	42.4 (19.6 to 72.7)	37.7 (23.5 to 57)	0.873
Length of stay in ICU (h)	70 (16 to 117)	66.5 (41 to 94)	0.750
Time to first sitting in chair (h)	48 (44 to 52)	46 (28 to 52.5)	0.067
Length of in-hospital stay (h)	240 (195 to 289)	216 (191 to 267)	0.085
Time to oxygen withdrawal (h)	93 (65 to 143)	86 (68 to 112)	0.750
Time to chest tube withdrawal (h)	65 (46 to 70)	64 (45 to 71)	0.990
Mechanical ventilation exceeding 24 h	5 (8.3)	0 (0.0)	0.058
Time from H0 to the first event (h)			
Extubation	8.4 (5.7 to 8.5)	7 (5 to 9.5)	0.195
Flatus	72 (44 to 100)	64 (44 to 100)	0.783
Faeces	100 (100 to 100)	80 (100 to 100)	0.087
Dietary intake	72 (40 to 100)	64 (44 to 100)	0.739
Oral medication intake	68 (28 to 100)	64 (40 to 100)	0.998
Nausea or vomiting	8 (13.3)	1 (1.8)	0.022
Postoperative pain (linear mixed model)[b]			
Sternal, at rest	1.34 ± [1.78]	1.03 ± [1.52]	0.035
Dorsal, at rest	0.96 ± [1.60]	0.95 ± [1.57]	0.984
Static (composite)	1.15 ± [1.39]	1.00 ± [1.30]	0.208
At measurement of CVP	2.63 ± [2.35]	2.30 ± [2.08]	0.167
At nursing care/mobilisation	3.36 ± [2.49]	2.74 ± [2.20]	0.018
During coughing	3.84 ± [2.43]	2.98 ± [2.30]	0.020
Dynamic (composite)	3.29 ± [1.98]	2.72 ± [1.87]	0.033
Morphine consumption (mg)[c]	45 (33.5 to 61.5)	43 (25 to 56)	0.160
Patient's satisfaction			<0.0001
Very bad	1 (1.7)	0 (0.0)	
Bad	1 (1.7)	0 (0.0)	
Average	9 (15.3)	2 (3.7)	
Good	32 (54.2)	14 (25.9)	
Very good	16 (27.1)	38 (70.4)	

Postoperative recovery outcomes of control and BLS groups (per-protocol analysis). Numerical data are expressed as mean ± SD or median (interquartile range). Categorical data are expressed as number of patients and percentage. H0 is the time of the patient's arrival in the ICU. BLS, bilateral sternal; CVP, central venous pressure. [a] In this analysis, there were 60 patients in the BLS group. [b] The displayed data are the grand means throughout the 72-h observation, and the *P* values are for the post hoc analyses (after significance was reached for all linear mixed models, $P < 0.0001$, with a time effect). [c] During the first 78 postoperative hours.

Study limitations

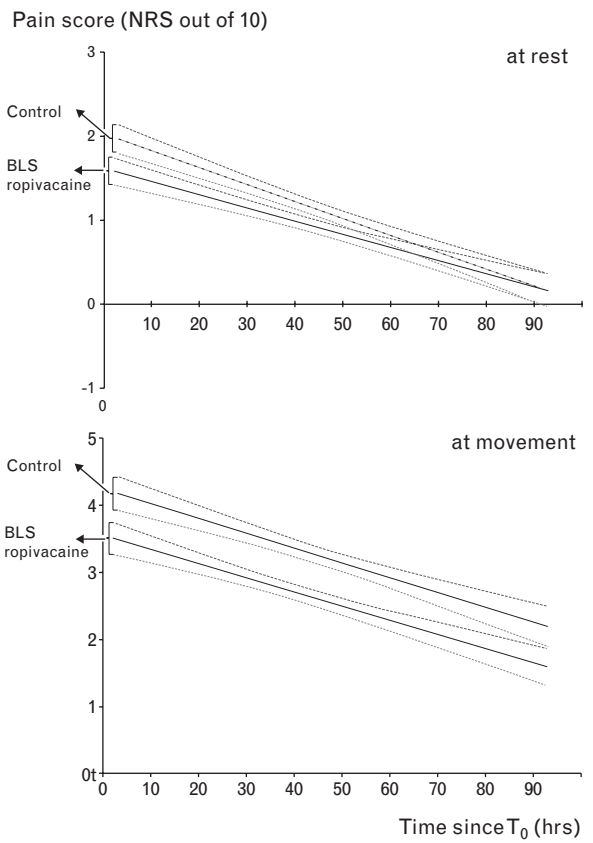
Our first motivation for an open design in the current study was the growing ethical issues raised by the use of an invasive placebo,[28] but such a design also has its limitations. We had already demonstrated the greater analgesic effect of the BLS infusion vs. placebo in a double-blind design,[19] and this was only a secondary outcome of the current study. Many clinical outcomes were analysed without knowledge of the treatment given. We specifically chose, as our primary outcome, the length of time to readiness for discharge from ICU as opposed to the actual LOS in the ICU, which is subject to nonmedical factors (e.g. patients eligible for discharge at the weekend are likely to stay until Monday), and therefore hard to compare with non-French practice. This explains why values for actual LOS were much higher than the blindly assessed time to readiness. With an open design however, we acknowledge that the effect could have been higher than it would have been if double-blind; conversely, the observed effect size is closer to real-life conditions. This leads us to the potential application of our results, as catheters for postoperative analgesia would incur a cost for the institutions and thus should be justified economically. Therefore, a cost/benefit analysis should be conducted in addition to our results, acknowledging that such analyses are highly dependent on the health system in which the study is undertaken. In such a study, too, greater statistical power to determine the effects on postoperative complications would be necessary.

We defined our patients at risk of respiratory complication on the basis of Wynne and Botti's review,[7] in which the most cited risk factors were age over 70 to 80, obesity, history of smoking and COPD (the other listed factors were exclusion criteria in our study). We preferred this to a risk score such as the ARISCAT,[13] which is not specific to cardiac surgery and does not provide a cut-off value to help decide who to exclude. The actual risk of respiratory complications in the control group was 23.3% in the current study, vs. 5.2% in nonselected patients.[19]

Safety issues

Safety is a major issue for postoperative local and regional techniques. Although such techniques for sternotomy have been effective in terms of pain control and narcotic requirements,[29,30] Agarwal *et al.*[31] reported that direct

Fig. 2



Time course of pain intensity at rest (top) and on movement (bottom). The linear regression curve of the composite scores for pain at rest plotted against the time of the patient's arrival in the ICU ('T0') with 95% confidence interval, for control and bilateral sternal groups.

Table 3 Postoperative complications

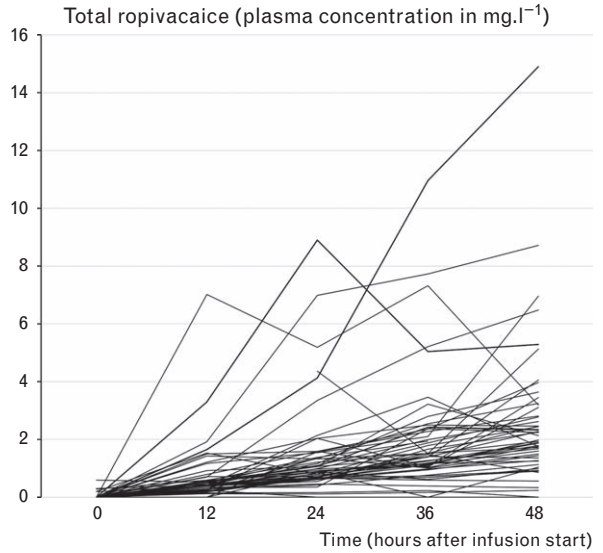
	Control ($n = 60$)	BLS ($n = 55$)	*P* value
In hospital			
Pulmonary complication[a]	14 (23.3)	4 (7.3)	0.021
Septicaemia	2 (3.3)	3 (5.5)	0.669
Wound infection	1 (1.7)	0 (0.0)	1.000
Mediastinitis	1 (1.7)	0 (0.0)	1.000
Extrapulmonary infection	11 (18.3)	5 (9.1)	0.184
Infection at any site	18 (30.1)	8 (14.6)	0.073
Cardiac arrhythmia			
Supraventricular	13 (21.7)	20 (36.4)	0.100
Ventricular	2 (3.3)	2 (3.6)	1.000
Need for pacemaker implantation	1 (1.7)	1 (1.8)	1.000
Myocardial infarction	0 (0.0)	0 (0.0)	1.000
Pulmonary embolism	0 (0.0)	1 (1.8)	0.478
Cardiac tamponade	2 (3.3)	0 (0.0)	0.497
Prolonged ileus	5 (8.3)	3 (5.5)	0.719
Mesenteric infarction	1 (1.7)	0 (0.0)	1.000
Peritonitis	1 (1.7)	0 (0.0)	1.000
Acute renal insufficiency	3 (5.0)	2 (3.6)	1.000
Delirium/mental confusion	13 (21.7)	2 (3.6)	0.005
Stroke	0 (0.0)	0 (0.0)	1.000
Prolonged stay or readmission to ICU	7 (11.7)	1 (1.8)	0.063
In-hospital death	1 (1.7)	2 (3.6)	0.606
Late postoperative survey (pain outcomes)[b]			
Delay after surgery (days)	199 ± 17	198 ± 36	0.549
Persistent sternal pain at rest[c]	4 (6.9)	3 (6.0)	0.850
Persistent sternal pain at movement	11 (19.0)[d]	17 (34.0)[e]	0.075
Persistent sternal neuropathic pain	1 (1.7)	1 (2.0)	1.000

Postoperative complications in control and BLS groups (per-protocol analysis). The late postoperative survey was conducted by phone call 6 months after surgery. Categorical data are expressed as number of patients and percentage. Numerical data are expressed as mean ± SD. BLS, bilateral sternal; NC, not calculated. [a] Defined according to the Melbourne Group Scale, that is, at least four of the following events = atelectasis or infiltration on chest X-ray, purulent sputum, physician diagnosis of pneumonia/chest infection, temperature >38°C, SpO_2 <90% on air, positive signs on sputum microbiology, white cell count >11.2 units or readmission/prolonged stay in ICU. [b] $n = 59$ and 50, respectively in control and intervention group, because of 1 and 5 losses to follow-up since discharge from hospital. [c] No case reported a pain score over 3/10. [d] 3 cases reported a pain score over 3/10. [e] 3 cases reported a pain score over 3/10.

infusion of ropivacaine into the sternal wound was associated with a 9.1% incidence of sternal wound infection. This complication can be a serious concern, especially in terms of responsibility for the surgical team. However, our BLS approach is theoretically devoid of such risk, as local anaesthetics are infused away from the sternal wound. This was confirmed in our study by the absence of infection in the treatment group, whereas one case of mediastinal infection was reported in the control group. The BLS infusion can also be performed in patients taking platelet inhibitors or with a high level of anticoagulation. Although TEA might offer superior analgesia, a systematic review by Landoni *et al.*[32] recently estimated the risk of epidural haematoma at 1 : 3552 patients. This, in our opinion, is not a negligible risk, particularly taking into account the trend for increased antiplatelet and anticoagulant treatments in this patient group since this review was conducted. Furthermore, the benefit vs. risk ratio of TEA also needs to be considered in terms of failure of catheter insertion (5.2%), malfunction of TEA (12.7%), logistic and manpower issues for catheter insertion before the day of surgery and consequently increased cost.[33] This may explain why only 7% of the anaesthetists caring for cardiac surgery patients use TEA in their practice.[34]

We cannot deny that our protocol led to high ropivacaine plasma levels. The BLS local anaesthetic was infused into tissues where drug absorption is slower than it would be in the pleura but, with good analgesia in mind, we chose a relatively high infusion rate (20 mg of ropivacaine as a loading dose, then 12 mg h^{-1}). As a result, the plasma level of ropivacaine exceeded 3.4 mg l^{-1}, the lowest value at which neurological symptoms have been observed in human volunteers,[35] in 22% of the treated patients. This compared with 5% in our previous study in which the doses were lower (10 mg then 8 mg h^{-1}).[19] The absence of any report of symptoms suggests that the risk of systemic toxicity was theoretical, although the sample size is too small to determine safety. Neurotoxicity has been reported after single-shot regional anaesthesia with ropivacaine, with total plasma levels that were often exceeded in the current study.[36,37] The apparent tolerance observed here can first be explained by continuous

Fig. 3



Time course of plasma concentration of total ropivacaine in the bilateral sternal infusion group. Each line represents one study participant; the line breaks correspond to missing values.

administration, which may reduce the redistribution of the drug.[38] Second, the values for the free fraction of ropivacaine are in general lower when measured in post-surgical conditions than in healthy volunteers, for example from 2 to 7.4%,[37,39–42] (13% for the mean values of the sample).[43] This is explained by greater plasma concentrations of proteins such as α1-acid glycoprotein after surgery,[39] leading to a higher bound fraction. Interestingly, low free fractions have been reported after blocks performed before surgery,[44] supporting the hypothesis that stress increases the α1-acid glycoprotein levels. However, the role of inflammation – and the resultant protective increase in other blood proteins – needs to be further explored, especially after cardiac surgery.

Conclusion

When given to patients at risk of respiratory complications, the BLS infusion provided benefits in terms of analgesia and other secondary outcomes, but it failed to reduce the length of time to readiness for discharge from ICU. Total plasma ropivacaine levels can exceed the theoretical toxic threshold, although it is difficult to determine the degree of clinically relevant risk. Before including this technique in a series of strategies aiming to improve analgesia and rehabilitation of cardiac surgery patients, more data are needed from a larger trial that consider safety and cost vs. benefit ratio.

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