The Analgesic Effects of a Bilateral Sternal Infusion of Ropivacaine After Cardiac Surgery

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Background and Objectives: The aim of this study was to assess the effects of a continuous postoperative administration of local anesthetic through 2 catheters placed deeply under fascia at the lateral edges of the sternum, close to the emergence of the intercostal nerves. We focused on pain during mobilization, as this aspect is likely to interact with postoperative morbidity.

Methods: Forty adult patients scheduled for open heart surgery with sternotomy were included in this randomized, placebo-controlled, double-blind study. A continuous fixed-rate infusion of 4 mL/hr of 0.2% ropivacaine or normal saline was administered during the first 48 postoperative hrs. All patients received acetaminophen and self-administered morphine. The efficacy outcomes were as follows: pain score during standardized mobilization and at rest; morphine consumption; spirometry and arterial blood gases; postoperative rehabilitation criteria, and patient satisfaction. Total ropivacaine plasma level was monitored throughout the study.

Results: Pain scores were lower in the ropivacaine group during mobilization ($P = 0.0004$) and at rest ($P = 0.0006$), but the analgesic effects were mostly apparent during the second day after surgery, with a 41% overall reduction in movement-evoked pain levels. The bilateral sternal block also reduced morphine consumption. It improved the patients' satisfaction and rehabilitation, but no effects were noted on respiratory outcomes. No major adverse effect due to the treatment occurred, but the ropivacaine plasma level was greater than 4 mg/L in 1 patient.

Conclusions: This technique may find a role within the framework of multimodal analgesia after sternotomy, although further confirmatory studies are needed.

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In the postoperative period, pain at rest may be relieved with the help of systemic analgesic treatments, including opiates. This is not true, however, for movement-evoked pain, which usually remains more severe than pain at rest and may be deleterious to postsurgical functional recovery.[1] This is the case for cardiac surgery, after which movement-evoked pain is likely to occur (due to deep breathing, coughing, central venous pressure measurement, and mobilization for nursing or physiotherapy) and may affect rehabilitation.[2,3] The use of epidural postoperative analgesia, despite its promising analgesic effects on movement-evoked pain,[4] is still a matter of debate because of safety issues after cardiac surgery.[5,6]

Of the possible local anesthetic techniques, single-injection peristernal techniques have a short-term effect,[7,8] whereas long-lasting peripheral blocks with continuous infusion of a local anesthetic solution in the operative site have shown promising results.[9–11] However, such infusion may risk impaired wound healing and local infection. Here, we present a proof-of-concept trial in which the effects of a bilateral sternal (BLS) nociceptive block (which aims to infuse local anesthetics at the termination of the intercostal nerves, close to the anterior branches of intercostal nerves at the lateral margins of the sternum[12]) were compared with placebo. We expected that the BLS block would reduce movement-evoked pain—measured during a standardized mobilization—after sternotomy.

METHODS

Study Design

This prospective randomized, placebo-controlled, double-blind, single-center trial was approved by the regional research ethics committee (CPP Sud-Est VI) and registered on ClinicalTrials.gov (no. NCT01196767). The inclusion criteria were adult patients, aged 18 to 90 years, scheduled for open-heart surgery with sternotomy for valve replacement or coronary artery bypass grafting with cardiopulmonary bypass (CPB). The exclusion criteria were as follows: emergency surgery, heart transplant, aortic dissection, additional thoracotomy, redo sternotomy, preoperative major left ventricular dysfunction, preoperative respiratory or renal insufficiency, pregnancy, incapacity to understand the

protocol and sign the consent or use patient-controlled analgesia (PCA), history of chronic use of opiates or drug addiction, and contraindication to any drug or material of the protocol. Patients received a detailed study explanation at preoperative consultation. The day before surgery, they gave their signed consent and were trained to report pain on a visual analog scale (VAS) and verbal numeric scale (VNS) from 0 to 10 and on how to use the PCA device. Spirometry was done with a handheld spirometer (MicroLoop; Micro Medical Ltd, Chatham Maritime, UK). Each patient was given an inclusion number to be used for the randomization, which was conducted by an independent research assistant with blocks of 4.

Anesthesia

General anesthesia was standardized as follows: premedication with hydroxyzine; monitoring with invasive blood pressure, 5-lead electrocardiography, bispectral index monitor, pulse-oxymetry, mechanomyography to assess myorelaxation (before induction), 4-port central jugular venous line, and urinary catheter (after induction); anesthesia induction with intravenously administered propofol, sufentanil, and cisatracurium; tracheal intubation, mechanical ventilation targeting a P_{ETCO_2} in the 27 to 32 mm Hg range, and Spo_2 greater than 95%; anesthesia maintenance targeting a bispectral index in the 40 to 60 range with propofol during CPB and sevoflurane otherwise, sufentanil (continuous infusion, started at 0.5 μg/kg per hour, then modulated according to hemodynamics and clinical signs of insufficient analgesia), and cisatracurium; antibiotic prophylaxis with cefuroxime and prevention of bleeding with tranexamic acid; and optimization of hemodynamics at the withdrawal of CPB with temporary tilt position, intravascular fluid loading, cardiac electrical pacing, or inotropic support, adapted to the observed situation.

Intervention: Bilateral Sternal Catheters

The catheters were inserted subcutaneously after the closure of sternotomy by the surgeon, with the help of the tunnelers entered lateral to xiphoid at subcostal margin and advanced upward, below the pectoral muscles over the costosternal margin parallel to the sternotomy incision (Fig. 1). The devices (I-Flow Corporation, Lake Forest, Calif) used to administer the study solution were as follows: 2 multihole catheters with a 12.5-cm diffusion area (ON-Q Soaker), inserted with the help of a 17-gauge × 8-in tunneler (ON-Q Tunneler Sheath) and connected by a Y-shaped tube to an elastomeric infusion pump with a reservoir of 270 mL (ON-Q Pain Buster). Steri-strips (3M France, Cergy-Pontoise, France) and wound dressing were used to secure the catheters. Before connection, the infusion pump was filled with the study solution under the control of the anesthesiologist in charge of the patient, who opened the allocation envelope. According to randomization, the study solution was either 0.2% ropivacaine (Naropeine 2 mg/mL; AstraZeneca, Rueil-Malmaison, France) or normal saline (Chlorure de Sodium; Aguettant, Lyon, France). A bolus of 5 mL per catheter of the study solution was injected after aspiration test before connection to the pump. The pump delivered a continuous infusion at a fixed rate of 4 mL/hr (ie, about 2 mL/hr through each catheter). All providers were blinded to the treatment group; the patient was unaware of the treatment administered, throughout the study. Nobody in the postoperative care unit (PACU) and surgical ward staff was aware of the treatment administered. Because the filling volume of the pumps for local anesthesia was supposed to provide an infusion for at least 48 hrs (mean expected duration, 67.5 hrs), pumps were not refilled, to avoid the risk of manipulation. The catheters were never removed sooner than the 48th hour after surgery. To reduce the number of painful interventions, catheter removal was usually concomitant with chest drain removal. The

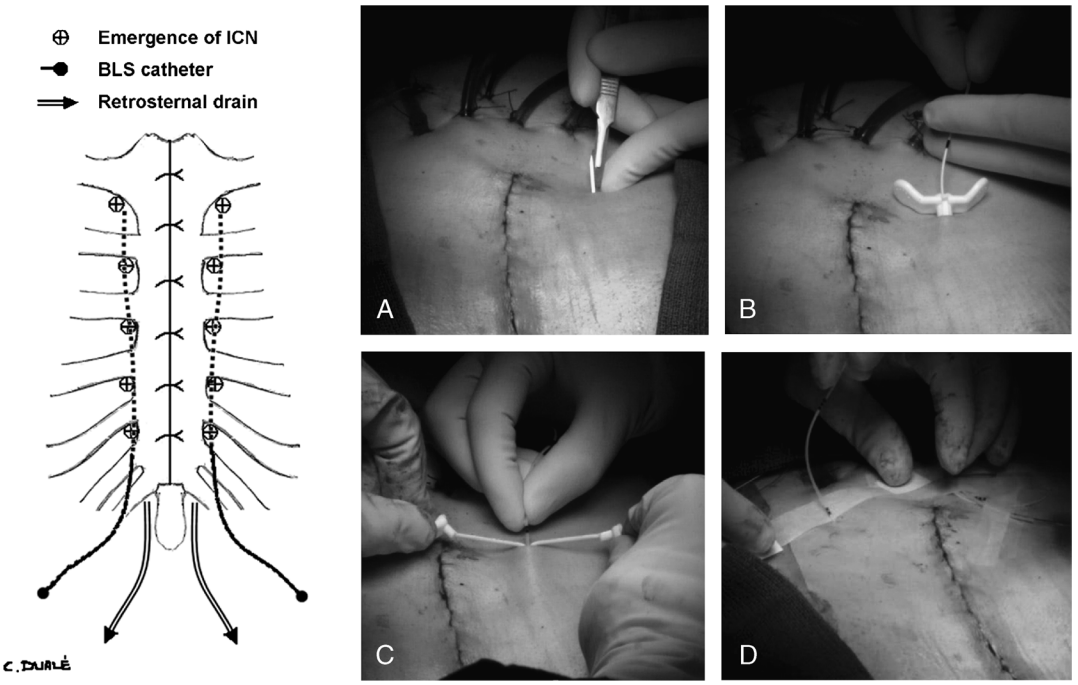

FIGURE 1. Description of the technique of BLS catheterization by the surgeon after surgery. Left, The BLS catheters are placed the closest possible to the emergence of the anterior branches of the intercostal nerves (ICN). Right, The catheters are inserted subcutaneously after skin closure. A, Skin incision lateral to xiphoid at subcostal margin. B, The Tunneler Sheath is advanced upward below the pectoral muscles over the costosternal margin parallel to the sternotomy incision. C, Sheath peeling. D, Fixation.

nursing staff was directed by a detailed protocol in the case report form to identify any sign of overdose of local anesthetic and, if such signs were noticed, to call the anesthesiologist on the ward. An intravenous rescue protocol that included oxygen therapy and intravenous lipids was planned.

Postoperative Care

Sedation was maintained with intravenously administered propofol during the transport from theater to and then until tracheal extubation. The mechanical ventilation in the PACU was maintained with the same parameters. Routine intensive care monitoring, chest radiography, and electrocardiography were performed as well as standard laboratory tests at T0, then daily and at the physician's request. Serum troponin (cTnI) was measured at least at T0, T0 + 6 hrs, and T0 + 12 hrs. Sedation was discontinued with the physician's approval when the patient's hemodynamic and respiratory parameters and core temperature were corrected and when neither active bleeding nor signs of cardiac ischemia were observed. Trachea was extubated once the patient could respond to simple commands and breathe spontaneously with good hemostasis. All patients were placed in a 30-degree sitting position, and postoperative analgesia was performed with 1 g of intravenously administered acetaminophen every 6 hrs and intravenously administered morphine chlorhydrate (Morphine; Aguettant). Morphine was initiated by the referent nurse in the PACU at the first patient demand; 3 mg intravenously per bolus was administered until the pain score went less than 3/10, then it was delivered via a PCA device (Vygon Frydom 5; Vygon, Ecouen, France). The PCA regimen was as follows: 1 mg/mL of isotonic saline, bolus = 1 mL, refractory period = 7 minutes, no continuous infusion.

The standard post–cardiac surgery care included: intravenously administered heparin, 50 IU/kg per day starting at the sixth hour after the end of surgery if no hemorrhage was noted and then increased on postoperative day (POD) 2 if indicated (ie, mechanical valve, for example); aspirin (250 mg/d for valve replacement and 75 mg/d otherwise); and ongoing antibiotic prophylaxis with cefuroxime for 48 hrs. Hemodynamics was optimized according to the patient's status, either by intravenous fluid loading, inotropic support, norepinephrine, or urapidil. The medication was administered orally if possible on POD 1, with priority administered to cardiovascular-targeted drugs and to the current medication. The patient was able to be transferred from the PACU to the surgical ward when none of the following supports were necessary: inotropic or vasopressive treatment, mechanical ventilation, dialysis, or life-threatening rhythm disturbance.

Measurement of Outcomes

T0 was the time of the patient's arrival in the PACU. The analgesia outcomes and the current vital parameters were recorded at T0 + 4 hrs, then every 4 hrs until T0 + 48 hrs. Pain was assessed on VAS and VNS at each regular observation time; it was first measured at rest then just after the patient was placed horizontally for the measurement of central venous pressure, as long as the patient stayed in the PACU. Pain was also measured just after each nursing session, when the patient was turned on their side. At T0 + 48 hrs, morphine consumption and patient satisfaction with pain control on a 4-point scale (0 = very unsatisfied, 1 = somewhat unsatisfied, 2 = rather satisfied, 3 = very satisfied) were noted. Sedation was quoted on a 4-point scale (0 = awake, 1 = still awake after verbal stimulus, 2 = sleepy and hardly answering to call, 3 = no answer at call). Nausea or vomiting was noted as an event (yes/no). In the case of nausea or vomiting, 8 mg of ondansetron were injected intravenously.

Bedside spirometry measurements were performed at the morning time of PODs 1 and 2. The first occurrence of flatus, feces, dietary intake, and oral medication intake since the morning of POD 1 was noted. On POD 2, the physiotherapist—who was in charge of every patient during the entire study—noted her perception of the patient's comfort, compliance to physiotherapy, and ability to early mobilization. Any occurrence of respiratory complication was noted by a physician.

Just before the beginning of BLS infusion and at 12, 24, 36, and 48 hrs after this point, blood samples for ropivacaine analysis were drawn. Only the samples taken from patients who received ropivacaine were analyzed. The total ropivacaine plasma concentration was measured by high-performance liquid chromatography after solid-phase extraction.

Six months after surgery, the patients were reached by phone and asked to answer a standardized questionnaire, in which they reported any sternal pain. If there was sternal pain, the patient was asked to describe it on a VNS of 10 and to respond to a DN4 questionnaire, a screening tool to identify neuropathic processes.[13]

Data Treatment

The pain score on VAS (or VNS when only this score was available) was considered as the primary outcome to analyze the effects on analgesia. In some cases in the surgical ward, pain at mobilization was not assessed during placement in horizontal position for measurement of central venous pressure, but pain was assessed during placement in lateral position for nursing. For these observations, the pain score was adjusted according to the equation of the regression slope used to correlate pain in horizontal and lateral positions out of the available data from concomitant measures. For the analysis, the pain scores were kept as raw values using the linear mixed model (see below). The area under curve (AUC) for pain scores was also calculated for PODs 1 and 2, using the trapezoidal rule.

The quality of oxygenation was assessed by calculating the Pa_{O_2}/F_{IO_2} ratio, either from the raw data of F_{IO_2} (during mechanical ventilation) or the estimated F_{IO_2} (spontaneous breathing). When oxygen was delivered through a high-concentration mask, the estimated F_{IO_2} was 0.6, 0.7, 0.8, and 0.9 for oxygen rates (in liters per minute) of 6, 7, 8, and 9 or more, respectively. When it was delivered through a nasal cannula, the estimated F_{IO_2} was 0.24, 0.28, 0.32, 0.36, 0.4, and 0.44 for oxygen rates (in liters per minute) of 1, 2, 3, 4, 5, and 6, respectively. It was 0.21 when no oxygen was administered. The data from spirometry were first blindly reviewed by the physician in charge of analysis to obtain coherent values for the parameters to be studied, namely, forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1), FEV_1/FVC ratio (FEV_1%), tidal volume, inspiratory capacity, inspiratory reserve volume, and expiratory reserve volume. For final comparison between groups, relative values (% of the preoperative value) were calculated for each subject at each POD (1 and 2). A delay in the occurrence of the first dietary intake and oral medication intake was converted into a score, where 1 point corresponded to a half-day on a scale ranging from 6 (the earliest occurrence observed, the morning of POD 1) to 0 (no event occurred at the 48th postoperative hour). The biologic outcomes were treated as follows: serum creatinine level was considered only at T0 + 12 hrs; for serum troponin level, an AUC was calculated based on the points T0, T0 + 6 hrs, and T0 + 12 hrs.

Statistical Analysis

The normality of the distribution was checked with a Shapiro-Wilk test. The quantitative data were expressed as mean ± SD if normally distributed and as median, interquartile

range, and range otherwise. The categorical data were expressed as the number of cases and percentage of the total. For simple comparisons between the 2 groups, the Student *t* test (numerical Gaussian), the Mann-Whitney *U* test (other numerical or ordinal), and the χ^2 or Fisher exact test (categorical) were used. Multivariate analysis using linear mixed models was performed to assess the evolution of pain scores (at rest and mobilization) for different groups. In these models, we always considered random subject effects: random intercept and slope. The residual normality was checked for all models presented in this article. The observation at T0 + 4 hrs was not considered for the analysis of pain scores because most of the patients were still under anesthesia at this point. Because the arterial line was withdrawn in many patients on day 2 after surgery, the between-groups comparisons for arterial blood gases were done only twice during the study, that is, T0 + 12 and T0 + 20 hrs. As the data from spirometry were already percentages of the baseline level, only comparisons between groups at the 2 times of measurements were made. The type I error was set at 5%. Analyses have been made under StataCorp (2007; Stata Statistical Software: Release 10, Stata Corporation, College Station, Texas) and XLStat (Addinsoft, Paris, France) plus Microsoft Excel 2003. Figures were generated using Microsoft Office Excel 2003, Paint 2003, and PowerPoint 2003 (Microsoft, Redmond, Washington).

The primary goal was to assess the superiority of the analgesia provided by BLS administration of ropivacaine compared with the placebo during standardized mobilization of the patient. With morphine self-administered in both groups, we did not hypothesize a superior analgesia at rest. Morphine consumption was a secondary outcome, as were all of the tolerance and satisfaction outcomes. The primary outcome was the pain score, the assumption being that the linear mixed model would define the times when a significant effect would be found, without inflation of the type I error. However, the sample-size calculation was made on the basis of a pain score of 5.2 ± 2 (VAS of 10) noted during the measurement of CVP at T0 + 24 hrs, taken from preliminary, unblinded observations data from our unit, including 150 measurements in 21 patients. We estimated that the BLS analgesia would provide a 50% reduction in the pain score, this effect size being that of morphine on pain scores at rest, in the same sample. With $\alpha = 5\%$, $1\text{-}\beta = 95\%$, and a bilateral hypothesis, the necessary sample size was estimated at 16 per group, which was increased to 20 per group for possible loss to follow-up and to increase power on secondary outcomes.

RESULTS

Of the 40 patients included in the study and randomized (20 in each group), 1 patient in the placebo group had a delayed pericardial hemorrhage between T0 + 12 hrs and T0 + 16 hrs and required emergency resurgery. The catheters were withdrawn, and the patient was excluded from the analysis of the

TABLE 1. Description of the Groups

	Ropivacaine (n = 20)	Placebo (n = 20)	*P*
Preoperative characteristics			
Age, y	68 ± 13	64 ± 12	0.416
Height, cm	170 ± 9	168 ± 10	0.382
Weight, kg	77 ± 9	76 ± 14	0.669
BMI, kg/m^2	27 ± 3	27 ± 4	0.917
Sex: female	3 ± 15	9 ± 45	0.038*
Euroscore	3 [1–6] (0–9)	4 [1.8–5.3] (0–8)	0.902
FEV_1 (% of predicted)	97 ± 21	90 ± 22	0.325
FVC (% of predicted)	94 ± 21	92 ± 22	0.810
FEV_1/FVC% (raw value), %	80 ± 8	77 ± 10	0.264
Surgery and anesthesia			
Total duration of surgery, min	272 ± 67	247 ± 69	0.261
Total dose of intraoperative sufentanil, μg	171 ± 48	158 ± 50	0.422
Valve replacement (all types)	9 (45)	14 (70)	0.110
Coronary bypass	14 (70)	7 (35)	0.027*
Type of ventilation at T0 + 4 hrs			0.534
Assist-controlled	12 (60)	16 (80)	
Bilevel positive airway pressure	5 (25)	2 (10)	
Pressure support	2 (10)	1 (5)	
Spontaneous + high-concentration oxygen	1 (5)	1 (5)	
Tidal volume†	561 ± 124	554 ± 92	0.833
Arterial blood gases at T0 + 4 hrs			
Pao_2/Fio_2, mm Hg	310 ± 82	333 ± 75	0.192
$Paco_2$, mm Hg	37.7 ± 6.8	36.0 ± 4.8	0.348
pH	7.33 ± 0.06	7.34 ± 0.07	0.587
HCO_3^-, mmol/L	19.4 ± 2.8	19.2 ± 3.0	0.842

Initial characteristics of the patients, according to the group of randomization. Numerical data are expressed as mean ± SD or median [interquartile range] (range). Categorical data are expressed as number (%) of patients.

*$P < 0.05$.

†Excluding the 2 nonventilated patients.

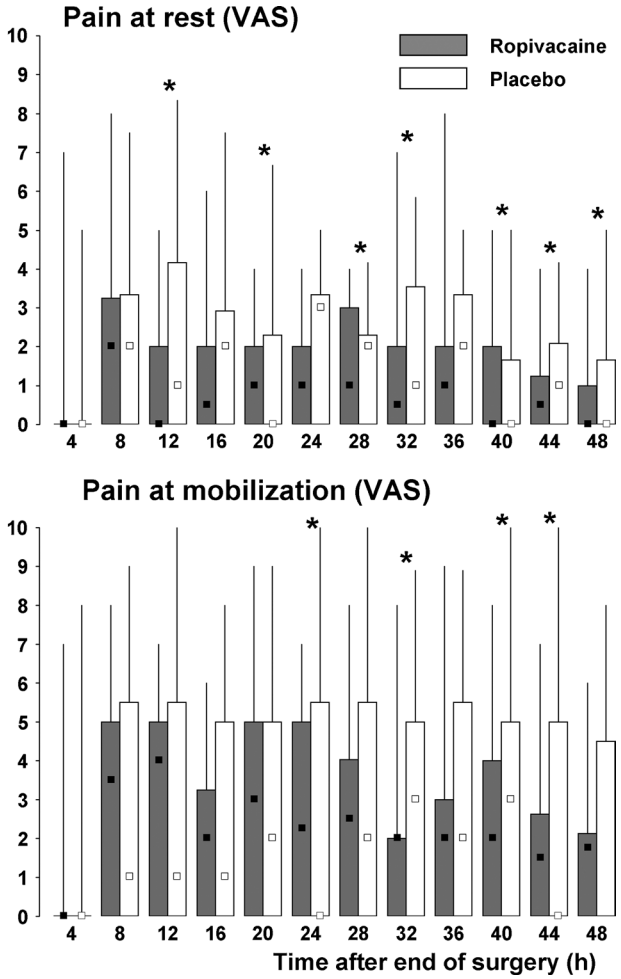

FIGURE 2. Time course of pain scores at rest (top) and standardized mobilization (bottom) during the first 48 hrs after the end of surgery, measured by VAS (10-point scale). The limits of the boxes represent the interquartile range, the limits of the whiskers represent the range, and the small square represents the median value, for each group at each time of measurement. The gray and the white boxes (black and white squares) represent the ropivacaine group and the placebo group, respectively. *Significant effect ($P < 0.05$) of the interaction (group × time) shown by the post hoc analyses of the linear mixed model, with time T0 + 8 hrs taken as reference and T0 + 4 hrs not kept in the analysis.

effects of treatment. Table 1 shows the characteristics of the patients, according to the group of randomization. The quality of randomization was good, although there were more women in the placebo group and more procedures for coronary bypass in the ropivacaine group. For the 23 patients who had a valve replacement, the types of replacement were as follows: aortic mechanical (n = 13), aortic biologic (n = 8), aortic biologic plus mitral (n = 1). No intervention on the ascending aorta or surgical treatment of arrhythmia was performed in the study. All patients who underwent coronary bypass, except 1 (in the placebo group), had internal mammary artery harvesting.

Table 2 and Figure 2 show the quality of postoperative analgesia in the 2 groups. The multivariate analysis of pain scores at rest was first done with [group × time] interaction as a factor. When no effect in interaction was found ($P = 0.090$), the model was tested without interaction. The model was found to be predictive ($P = 0.0006$), with a significant effect on the group (ie, the treatment tested; $P < 0.0001$) and time of observation ($P = 0.032$). For the analysis of pain scores at mobilization, the model was also predictive ($P = 0.0004$), with a significant effect on the time in observation ($P < 0.0001$) and [group × time] interaction ($P < 0.0001$), which can be interpreted as an effect of treatment. As shown in the diagram (Fig. 2) and the AUCs (Table 2), the effects of treatment were mostly apparent on POD 2. The effect size of the BLS block was a reduction of 41% in the AUC of pain at mobilization on POD 2. There was also less morphine consumption in the ropivacaine group.

For 1 patient in the placebo group, no spirometric measurement had been done on POD 1; for 1 patient in the ropivacaine group on POD 2, the spirometric data could not be interpreted because of mental confusion. Table 3 shows that most of the studied parameters were impaired during the 2 first PODs and that the rate of impairment was similar in both groups. Similarly, no major effect of the treatment was observed in the arterial blood gases. Clinical tolerance and comfort were better in the ropivacaine group (Table 4). Spearman analyses of correlation between satisfaction scores and pain scores showed an inverse correlation, with $\rho = -0.272$ (95% confidence interval, -0.541 to -0.047) for pain at rest and $\rho = -0.357$ (confidence interval, -0.604 to -0.047) for pain during mobilization. Table 4 also shows the results of the survey at the sixth month after surgery; no difference was found in terms of persistent pain. The rate of persistent pain observed in the whole sample of the present study (15.8%) was significantly less ($P = 0.033$) than the 28% rate reported in a large prospective survey 1 year after surgery (90 of 318 cases).[14]

Eight of the 100 available samples for ropivacaine could not be analyzed because of interference with no possible

TABLE 2. Quality of Postoperative Analgesia

	Ropivacaine (n = 20)	Placebo (n = 19)	*P*
Morphine consumption during the first 48 postoperative hrs, mg	20 [18–32] (12–79)	30 [25–39] (14–104)	0.036*
Pain at rest: AUC			
From T0 + 4 hrs to T0 + 24 hrs	18 [12–39] (0–44)	24 [16–42] (0–110)	0.331
From T0 + 24 hrs to T0 + 48 hrs	25 [12–41] (0–84)	44 [20–66] (0–114)	0.100
Pain at mobilization: AUC			
From T0 + 4 hrs to T0 + 24 hrs	43 [36–56] (0–94)	44 [22–60] (0–116)	0.888
From T0 + 24 hrs to T0 + 48 hrs	47 [29–74] (0–166)	102 [44–131] (8–172)	0.025*

Data are expressed as median [interquartile range] (range).
*$P < 0.05$.

TABLE 3. Respiratory Postoperative Outcomes

		Ropivacaine (n = 20)	Placebo (n = 20)	*P*
Type of ventilation				
At T0 + 12 hrs	Assist-controlled	0 (0)	2 (10)	0.391
	Bilevel positive airway pressure	1 (5)	0 (0)	
	Pressure support	0 (0)	1 (5)	
	Spontaneous + high-concentration oxygen	11 (55)	10 (50)	
	Spontaneous + oxygen on nasal cannula	8 (40)	7 (35)	
At T0 + 20 hrs	Bilevel positive airway pressure	1 (5)	0 (0)	0.555
	Pressure support	0 (0)	1 (5.3)	
	Spontaneous + high-concentration oxygen	5 (25)	4 (21.1)	
	Spontaneous + oxygen on nasal cannula	14 (70)	14 (73.7)	
Arterial blood gases*				
At T0 + 12 hrs	Pao_2/Fio_2, mm Hg	255 ± 93	294 ± 104	0.226
	$Paco_2$, mm Hg	38.7 ± 5.8	39.4 ± 6.4	0.726
	pH	7.33 ± 0.05	7.32 ± 0.05	0.411
	HCO_3^-, mmol/L	20.0 ± 2.3	19.8 ± 2.6	0.819
At T0 + 20 hrs	Pao_2/Fio_2, mm Hg	276 ± 121	304 ± 108	0.489
	$Paco_2$, mm Hg	35.6 ± 5.4	38.0 ± 4.3	0.161
	pH	7.37 ± 0.05	7.36 ± 0.05	0.460
	HCO_3^-, mmol/L	20.1 ± 2.3	21.1 ± 2.3	0.281
Postoperative spirometry†‡				
On POD 1	FEV_1	40 [30–53] (22–65)	42 [31–48] (6–70)	1.000
	FVC	39 [33–51] (18–63)	38 [35–46] (18–63)	0.989
	FEV_1%	106 [101–114] (56–142)	109 [103–113] (11–137)	0.779
	IC	34 [26–43] (21–63)	42 [29–45] (17–88)	0.182
	TV	68 [62–95] (44–183)	80 [66–94] (45–129)	0.623
	IRV	19 [10–29] (0–41)	22 [13–38] (1–100)	0.227
	ERV	48 [15–110] (0–193)	40 [16–78] (0–144)	0.593
On POD 2	FEV_1	40 [35–57] (22–72)	35 [27–45] (15–71)	0.292
	FVC	37 [29–47] (18–77)	36 [25–43] (13–67)	0.332
	FEV_1%	104 [98–117] (72–130)	109 [103–114] (93–147)	0.319
	IC	36 [27–58] (0–73)	40 [30–43] (13–68)	0.966
	TV	68 [61–109] (39–147)	84 [65–108] (47–133)	0.527
	IRV	22 [13–35] (0–74)	21 [12–31] (0–65)	0.747
	ERV	35 [12–80] (0–265)	28 [9–44] (0–124)	0.304

Numerical data are expressed as mean ± SD or median [interquartile range] (range). Categorical data are expressed as number (%) of patients.

POD 1, 1st postoperative day; POD 2, 2nd post-operative day; FVC, vital capacity; FEV_1, forced expiratory volume in 1 second; FEV_1%: FEV_1/FVC ratio; TD, tidal volume; IC, inspiratory capacity; IRV, inspiratory reserve volume; ERV, expiratory reserve volume.

$P < 0.05$.

*Missing data (see Results): 3 in the ropivacaine group, 2 in the placebo group.

†Missing data (see Results): 1 in the placebo group.

‡All the data out of spirometry are expressed as percentage of the preoperative value for each patient, taken as baseline.

correction (n = 4), too small of a sample (n = 3), and altered plasma (n = 1). The values for total ropivacaine plasma concentration are displayed on Figure 3. It shows that the treatment had been administered in all the allocated patients. A trend toward increased concentrations with time was noted, with a mean slope of 0.03 mg/L per hour. The value of 3.4 mg/L, that is, the lowest value for which neurologic symptoms have been observed in human volunteers,[15] was surpassed in 1 patient since T0 + 12 hrs, although no symptom of overdose was noted.

DISCUSSION

Three trials studying a local anesthetic solution applied directly to the sternotomy incision after surgery have been published.[9–11] In all of these double-blind and placebo-controlled trials, 2 catheters were set immediately above the wired sternum, and the administration rate of the solution was 4 mL/hr from an elastomeric pump, providing a 40- to 48-hr-long administration. In 1 study, the drug tested was bupivacaine, 0.25% and 0.5%[10]; in the other 2 studies, ropivacaine was preferred for safety reasons, and the concentration tested was 0.2%[9] or 0.3375%.[11] All studies showed that the technique reduced pain at rest and opiate consumption. Beneficial effects of the treatment on other morbidity outcomes or length of stay in the hospital were also noted, although the benefits were not always significant.[9–11] No serious adverse event was reported, but in 1 study in which 2 catheters were placed in 2 different planes of the sternotomy wound, a high incidence of catheter-related problems, such as unintentional

TABLE 4. Other Clinical and Biologic Postoperative Outcomes

	Ropivacaine (n = 20)	Placebo (n = 19)	*P*
Early outcomes (48 first postoperative hrs)			
Sedation score >1*	13/200 (6.5)	26/188 (13.8)	0.016†
Sedation score >2*	3/200 (1.5)	2/188 (1.1)	0.944
Nausea or vomiting‡	5 (25)	4 (21.1)	1.000
Flatus‡	19 (95)	16 (84.2)	0.267
Feces‡	2 (10)	0 (0)	0.157
First dietary intake§	5 [0–6] (0–6)	0 [0–3.5] (0–6)	0.0105†
First oral medication intake§	5 [4–6] (3–6)	4 [4–5] (0–6)	0.0361†
Early mobilization‡	13 (65)	1 (5.3)	0.0004†
Patient involved in physiotherapy‖	12 (60)	5 (26.3)	0.097
Good comfort for the patient‖	15 (75)	5 (26.3)	0.0077†
Postoperative complication	1 (5)	2 (10.5)	0.605
Postoperative complication (description)			NA
Difficulty to cough	1	0	
Bronchial hypersecretion	0	1	
Mental confusion plus ileus	0	1¶	
Patient's personal satisfaction			<0.0001†
Very unsatisfied	0 (0)	0 (0)	
Somewhat unsatisfied	0 (0)	8 (42.1)	
Rather satisfied	7 (35)	10 (52.6)	
Very satisfied	13 (65)	1 (5.3)	
Serum creatinine at T0 + 12 hrs (μmol.l-1)	76 ± 26	78 ± 28	0.779
Serum troponin between T0 and T0 + 12 hrs (AUC)	3.6 [2.9–4.5] (2.3–31.9)	3 [2.1–6] (1–17)	0.527
Long-term follow-up (phone call)			
Delay after surgery (days)	184 ± 2	184 ± 1	0.715
Deceased	1 (5)	0 (0)	1
Sternal persistent pain	3 (15.8)	3 (15.8)	1
Pain scores (VAS out of 10)#	2 ± 0	3.7 ± 0.9	0.059
Sternal persistent pain with positive DN4#	0 (0)	1 (33)	0.273

Categorical data are expressed as number (%) of patients. Numerical data are expressed as median [interquartile range] (range).

*Number of observations from T0 + 12 hrs to T0 + 48 hrs.

†$P < 0.05$.

‡Number of patients within the 48 first postoperative hrs.

§Score (see Methods for definition).

‖According to the physiotherapist.

¶See Results for details.

#Only for patients reporting sternal persistent pain.

NA indicates not applicable.

removal during dressing changes and 1 case of catheter breakage at removal, was noted.[10] The promising results of these proofs of concept might have led to a validation trial with a sample size large enough to study more relevant efficacy outcomes and safety. However, a risk of impaired cicatrisation and infection may be argued, illustrated by the recent discontinuation of a trial because of increased wound infection rate.[16]

For these reasons, we were interested in an infusion technique proposed by Jeffrey Milliken, MD (University of California, Irvine Medical Center, Orange, California), for which no comparative study had been done about the analgesic effects. The aim of this BLS block is to target the anterior branches of the second to the sixth intercostal nerves that innervate the sternum and reach the skin near the midline immediately lateral to the sternal margin, thus at a safe distance from the wound.[7,12] We chose ropivacaine because (1) it has been considered safer than bupivacaine[17]; (2) presternal bupivacaine, at a significantly effective concentration (0.5%), led to quite high bupivacaine serum levels[10]; and (3) good analgesia was provided with presternal administration of ropivacaine.[9,11] The 0.2% concentration of ropivacaine was the smallest effective block in the presternal studies.[9,11] The administration rate was kept the same as in previous studies, that is, 4 mL/hr.[9–11] The 270-mL elastomeric pump allowed at least 48 hrs of administration without need of refilling, which avoided manipulations that could increase the risk of infection.

Here, we showed promising effects of the BLS postoperative block on pain during mobilization and a tendency toward improved quality of rehabilitation, although this latter point must be interpreted with caution, as the study was not designed to measure such outcomes. In comparison, the infusion of local anesthetic close to the wound (1) is more likely to induce complications (see above) and (2) has not been tested on movement-evoked pain, although such assessment seems necessary in the

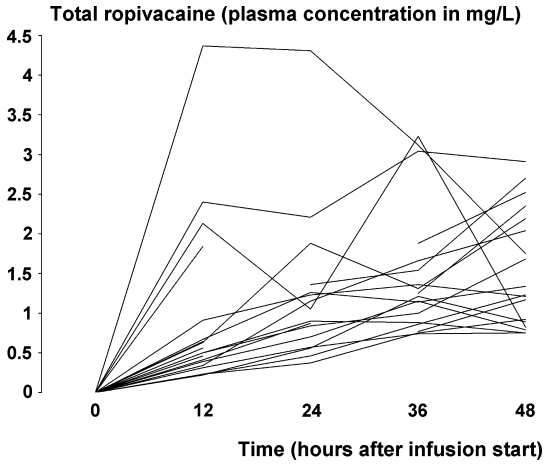

FIGURE 3. Time course of plasma concentration of total ropivacaine, in the group having received the drug. Each line represents 1 subject; the line discontinuations correspond to missing values.

field of postoperative care.[1] The BLS block, nonetheless, appeared to be effective only after the 20th postoperative hour, suggesting that this postoperative time is crucial to the patient and rehabilitation. This is consistent with the observation of a large cohort of post–cardiac surgery patients, where there was a peak of movement-induced pain during the first day following the day of surgery.[18] Further improvement of the technique might be obtained with an earlier onset of analgesia, either by increasing the catheter's length of insertion for a better diffusion or by a greater loading dose before connecting the catheter to the pump. In addition, it is difficult to know whether the effects observed in the patients' ability to follow a rehabilitation program were due to the quality of analgesia or systemic effects of the local anesthetic drug, as already observed with intravenous lidocaine.[19]

As stated above, the small sample size of this pilot trial is its main limitation, especially for interpretation of results on outcomes with a low incidence rate such as long-term morbidity. This is also true for persistent postsurgical pain; we must point out that we were not expecting a preventive effect for this type of pain, but it was assessed to determine whether BLS catheterization was likely to induce per se neuropathic complications, which would have compromised its future use. Finally, the sample size may explain the imbalance between groups (for sex ratio and rate of bypasses); this may not have influenced the results, but it suggests that further confirmation trials should consider a stratification of these parameters.

The impairment of postoperative pulmonary function tests was expected.[20] However, the improvement of analgesia by BLS ropivacaine was not linked to better hemostasis or pulmonary function. The difficulties in performing these inquiries during the early postoperative period may have influenced the quality of the results, but the main explanation for such failure is that pain was a minor factor in the respiratory dysfunction observed after sternotomy.[21]

The levels and time course of the ropivacaine plasma levels could be interpreted positively, as these remained beneath the mean level observed for occurrence of neurologic symptoms in humans (unbound drug: 0.6 μg/mL, ie, ≈5 μg/mL of total drug).[17] The safety issue must be addressed, however, as (1) neurologic symptoms may occur at lower levels[15,17]; (2) the mean limit was surpassed in 1 patient; and (3) there was a trend toward increased levels with time, suggesting a risk of toxicity in case of administration for a longer time or with higher doses. Such levels have recently been reported after transversus abdominis plane block.[22] The risk of toxicity may be lower in the postoperative context because inflammation increases the level of circulating proteins and may lower the free ropivacaine plasma concentration.[23–25]

In conclusion, a 48-hr infusion of BLS ropivacaine improved postoperative analgesia at rest and during mobilization. These effects were shown mainly during the second day after surgery, but the quality of rehabilitation (except for respiratory outcomes) was also improved. Large-sample studies are now needed to give precision about safety and efficacy on postoperative morbidity. It would be interesting, too, to focus on a subpopulation of patients, such as obese or elderly individuals, for whom an impaired quality of rehabilitation may have severe consequences.

REFERENCES

1. Srikandarajah S, Gilron I. Systematic review of movement-evoked pain versus pain at rest in postsurgical clinical trials and meta-analyses: a fundamental distinction requiring standardized measurement. *Pain*. 2011;152:1734–1739.
2. Chaney MA. How important is postoperative pain after cardiac surgery? *J Cardiothorac Vasc Anesth*. 2005;19:705–707.
3. Van Gulik L, Ahlers SJ, Brkic Z, et al. Improved analgesia after the realisation of a pain management programme in ICU patients after cardiac surgery. *Eur J Anaesthesiol*. 2010;27:900–905.
4. Werawatganon T, Charuluxanun S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. *Cochrane Database Syst Rev.* 2005:CD004088.
5. Svircevic V, van Dijk V, Nierich AP, et al. Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery. *Anesthesiology.* 2011;114:271–282.
6. Clemente A, Carli F. The physiological effects of thoracic epidural anesthesia and analgesia on the cardiovascular, respiratory and gastrointestinal systems. *Minerva Anestesiol*. 2008;74:549–563.
7. Barr AM, Tutungi E, Almeida AA. Parasternal intercostal block with ropivacaine for pain management after cardiac surgery: a double-blind, randomized, controlled trial. *J Cardiothorac Vasc Anesth*. 2007;21:547–553.
8. Kocabas S, Yedicocuklu D, Yuksel E, Uysallar E, Askar F. Infiltration of the sternotomy wound and the mediastinal tube sites with 0.25% levobupivacaine as adjunctive treatment for postoperative pain after cardiac surgery. *Eur J Anaesthesiol*. 2008;25:842–849.
9. Dowling R, Thielmeier K, Ghaly A, et al. Improved pain control after cardiac surgery: results of a randomized, double-blind, clinical trial. *J Thorac Cardiovasc Surg*. 2003;126:1271–1278.
10. White PF, Rawal S, Latham P, et al. Use of a continuous local anesthetic infusion for pain management after median sternotomy. *Anesthesiology.* 2003;99:918–923.
11. Koukis I, Argiriou M, Dimakopoulou A, et al. Use of continuous subcutaneous anesthetic infusion in cardiac surgical patients after median sternotomy. *J Cardiothorac Surg*. 2008;3:2.
12. McDonald SB, Jacobsohn E, Kopacz DJ, et al. Parasternal block and local anesthetic infiltration with levobupivacaine after cardiac surgery with desflurane: the effect on postoperative pain, pulmonary function, and tracheal extubation times. *Anesth Analg*. 2005;100:25–32.
13. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*. 2005;114:29–36.
14. Meyerson J, Thelin S, Gordh T, Karlsten R. The incidence of chronic post-sternotomy pain after cardiac surgery—a prospective study. *Acta Anaesthesiol Scand*. 2001;45:940–944.

15. Naropin. RxList—The Internet Drug Index. Available at: http://www.rxlist.com/naropin-drug.htm. Accessed October 10, 2011.
16. NCT00586976. A phase II/III study of continuous local anesthetic infusion in median sternotomy following cardiac surgery. ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT00586976?term=mayo+clinic+ropivacaine&rank=2. Accessed October 10, 2011.
17. Knudsen K, Beckman SM, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth*. 1997;78:507–514.
18. Milgrom LB, Brooks JA, Qi R, et al. Pain levels experienced with activities after cardiac surgery. *Am J Crit Care*. 2004;13:116–125.
19. Saadawy IM, Kaki AM, Abd El Latif AA, Abd-Elmaksoud AM, Tolba OM. Lidocaine vs. magnesium: effect on analgesia after a laparoscopic cholecystectomy. *Acta Anaesthesiol Scand*. 2010;54:549–556.
20. Chetta A, Bobbio A, Aiello M, et al. Changes in lung function and respiratory muscle strength after sternotomy vs. laparotomy in patients without ventilatory limitation. *Eur Surg Res*. 2006;38:489–493.
21. Wynne R, Botti M. Postoperative pulmonary dysfunction in adults after cardiac surgery with cardiopulmonary bypass: clinical significance and implications for practice. *Am J Crit Care*. 2004;13:384–393.
22. Griffiths JD, Barron FA, Grant S, et al. Plasma ropivacaine concentrations after ultrasound-guided transversus abdominis plane block. *Br J Anaesth*. 2010;105:853–856.
23. Wulf H, Worthmann F, Behnke H, Bohle AS. Pharmacokinetics and pharmacodynamics of ropivacaine 2 mg/mL, 5 mg/mL, or 7.5 mg/mL after ilioinguinal blockade for inguinal hernia repair in adults. *Anesth Analg*. 1999;89:1471–1474.
24. Wiedemann D, Muhlnickel B, Staroske E, Neumann W, Rose W. Ropivacaine plasma concentrations during 120-hour epidural infusion. *Br J Anaesth*. 2000;85:830–835.
25. Pettersson N, Emanuelsson BM, Reventlid H, Hahn RG. High-dose ropivacaine wound infiltration for pain relief after inguinal hernia repair: a clinical and pharmacokinetic evaluation. *Reg Anesth Pain Med*. 1998;23:189–196.