European Journal of Cardio-Thoracic Surgery Advance Access published March 11, 2015

European Journal of Cardio-Thoracic Surgery (2015) 1–9
doi:10.1093/ejcts/ezv097

ORIGINAL ARTICLE

Cite this article as: Fiorelli A, Izzo AC, Frongillo EM, Del Prete A, Liguori G, Costanzo ED *et al*. Efficacy of wound analgesia for controlling post-thoracotomy pain: a randomized double-blind study. Eur J Cardiothorac Surg 2015; doi:10.1093/ejcts/ezv097.

THORACIC

Efficacy of wound analgesia for controlling post-thoracotomy pain: a randomized double-blind study†

Alfonso Fiorelli[a], Anna Cecilia Izzo[a], Elisabetta Maria Frongillo[a], Assunta Del Prete[a], Giovanni Liguori[b], Emilio Di Costanzo[c], Giovanni Vicidomini[a] and Mario Santini[a,*]

[a] Thoracic Surgery Unit, Second University of Naples, Naples, Italy
[b] Anestesiology and Intensive Care Unit, Cardarelli Hospital, Naples, Italy
[c] Anestesiology and Intensive Care Unit, Monaldi Hospital, Naples, Italy

* Corresponding author. Chirurgia Toracica – Seconda Università di Napoli, Piazza Miraglia, 2, I-80138 Naples, Italy. Tel: +39-0815665228; fax: +39-0815665230; e-mail: mario.santini@unina2.it (M. Santini).

Received 31 October 2014; received in revised form 4 February 2015; accepted 5 February 2015

Abstract

OBJECTIVES: Continuous wound infusion of local anaesthetics has been successfully applied for postoperative pain control in several procedures but, surprisingly, it is underused in thoracic surgery. We aimed to investigate the effects of wound analgesia associated with systemic patient-controlled analgesia in patients undergoing lung cancer resection with muscle-sparing thoracotomy.

METHODS: Sixty consecutive patients undergoing lung cancer resection via standard muscle-sparing thoracotomy were randomized into two groups (wound analgesia and placebo groups). Bupivacaine in the wound group and free-saline solution in the placebo group were injected using a multiholed catheter connected to an elastomeric pump inserted at the end of operation between the pericostal sutures and the serratus muscle and removed 48 h after. The inter-group differences were assessed by the following criteria: (i) level of cytokines [IL-6, IL-10 and tumour necrosis factor-alpha (TNF-alpha)]; (ii) pain on a visual analogue scale at rest and after coughing; (iii) recovery of respiratory functions (flow expiratory volume in 1 s % and forced vital capacity %) and (iv) narcotic medication consumption at different time points of the postoperative course.

RESULTS: Five out of a total of 60 patients were excluded from the final analysis. Thus, the wound and placebo groups comprised 27 and 28 patients, respectively. The wound group compared with the placebo group had a significant decrease of IL-6 ($P < 0.001$), IL-10 ($P < 0.001$) and TNF-alpha ($P < 0.001$) blood concentration levels, pain scores at rest ($P < 0.001$) and after coughing ($P = 0.01$), and a reduction of additional morphine intake ($P = 0.03$) and Ketorolac ($P = 0.01$) during the entire postoperative course. The recovery of the flow expiratory volume in one second % ($P = 0.01$) and the forced vital capacity % ($P = 0.02$) was also better in the wound than in the placebo group.

CONCLUSIONS: Our data prove that wound analgesia is an effective, easy and safe procedure. It significantly reduces systemic inflammatory markers, pain scores and opioid intake; and accelerates the recovery of respiratory function. Catheter placement does not require particular manoeuvres by the surgeon nor does the elastomeric pump need any adjustment or care by physicians or nurses.

Keywords: Wound analgesia • Thoracotomy • Local anaesthetic analgesia • Pain mediator • Thoracic surgery

INTRODUCTION

Acute pain is one of the most frequent complaints of patients after thoracotomy. Ineffective chest expansion due to a painful wound may predispose a patient to atelectasis, ventilation/perfusion mismatching, hypoxaemia and infection. This could lead to an increased rate of postoperative complications, a longer hospital stay and a more expensive medical treatment. The ideal analgesic technique should improve an effective secretion clearing with cough; moreover, it should allow an early mobilization, and thus reduce the length of hospital stay [1].

Various techniques for post-thoracotomy pain relief have been described but there is no internationally accepted policy on the best strategy. Systemic administration of opioids is the easiest and most common method to provide analgesia but it may be associated with several undesirable effects, such as respiratory depression, nausea, vomiting, ileus and urinary retention [2]. Epidural analgesia has emerged as the possible ideal analgesic procedure for thoracotomy pain management in the last years, but not all studies have shown that it improves pulmonary function and reduces pulmonary complications [3–5]. Inter-pleural, intrapleural

† Presented at the 22nd European Conference on General Thoracic Surgery, Copenhagen, Denmark, 15–18 June 2014.

or extrapleural administration of local anaesthetics (LAs) have been reported as valid alternatives to epidural analgesia; their application and management are easier and they are not associated with complications of opioids, but there is a high risk of toxic effects of LAs due the systemic absorption by pleura and intercostal nerves.

Therefore, alternative strategies for thoracotomy pain control are of considerable interest.

Recently, continuous wound infusion of LAs has been successfully applied for pain control after orthopaedic, abdominal, gynaecological, urological and plastic procedures [6–8], but their positive effects after a thoracic procedure are still unclear. The aim of the present study is to investigate the effects of wound analgesia associated with systemic patient-controlled analgesia (PCA) in patients undergoing non-small-cell lung cancer (NSCLC) resection via muscle-sparing thoracotomy.

MATERIALS AND METHODS

Study design

Our study is a prospective, double-blind, randomized, placebo-controlled, unicentre trial including a series of consecutive patients undergoing NSCLC resection via standard muscle-sparing thoracotomy at Thoracic Surgery Unit of Second University of Naples from January 2011 to December 2013.

We enrolled (i) patients aged 18 years or more, (ii) with American Society of Anesthesiology physical status between I and III and (iii) scheduled for lung resection via muscle-sparing thoracotomy without associated pleurectomy or chest wall resection.

Exclusion criteria were: (i) previous history of chronic pain; (ii) preoperative use of narcotics; (iii) previous thoracic procedures; (iv) recurrent operations; (v) neurological signs such as movement limitation or cerebral confusion with inability to comprehend or perform verbal and physical instructions; (vi) incision different from muscle-sparing thoracotomy, (vii) allergy to LAs or morphine and (vii) inclusion in other studies on pain management.

Patients recruited in the study were randomly allocated to receive a continuous surgical wound site infusion of either bupivacaine (wound group) or saline solution (placebo group) delivered by a multiholed wound catheter (PAINfusor by Baxter) connected with an elastomeric pump (ON-Q PainBuster, ref. PS6505; I-Flow Corp., Lake Forest, CA, USA) according to computer-generated codes kept in a sealed opaque envelope. All patients were provided with PCA according to the hospital standard of care for pain relief. At the end of surgery, the envelope was opened by an anaesthetist not involved in the anaesthetic management during surgery or in the postoperative assessment. To test the validity of wound analgesia, we evaluated the inter-group differences regarding (i) inflammatory mediators, (ii) visual analogue scale (VAS) scores; (iii) spirometric tests including flow expiratory volume in 1 s % (FEV1%) and forced vital capacity % (FVC%) expressed as a percent of predicted value and (iv) narcotic consumption at different time-points of the postoperative course.

Finally, the plasma bupivacaine concentration was also determined in order to prevent side-effects if the concentrations were close to the toxicity threshold. The study was approved by the Ethics Committee of our Institution and signed informed consent was obtained from all patients before enrolment.

Patient population

Sixty-seven consecutive patients with NSCLC undergoing surgical resection via standard muscle-sparing thoracotomy were eligible for the present study. Seven patients were excluded because of disagreement with the inclusion criteria ($n = 5$) and consent withdrawal ($n = 2$). Patients were randomly divided in two groups: the wound group ($n = 30$) and the placebo group ($n = 30$). Each patient was given a face-to-face detailed study explanation by the surgeon before enrolment. Patients were instructed the day before operation how to use the VAS scale and the PCA pump, and how to ask for additional medications in case of intolerable pain. Groups were assumed comparable because they had the same anaesthetic regimens and the surgical procedures were performed by the same experienced surgeon. Besides, recovery from anaesthesia and pain management immediately after surgery were identical for all patients. All investigators and study staff, including the nurses, were blinded to the elastomeric pump drugs.

Anaesthetic technique

Anaesthetic management was standardized in an attempt to eliminate the effects of different anaesthetic regimens on postoperative pain levels. All patients received general anaesthesia premedication with 5–10 mg diazepam one hour before surgery, induction with thiopentone, selective intubation following succinylcholine and maintenance with pancuronium, nitrous oxide, oxygen and a volatile inhalational agent (isoflurane or enflurane). Intraoperative fentanyl administration was limited to 2 μg/kg at the time of skin incision and then 1 μg/kg every hour at the anaesthetist's discretion, depending on the duration of surgery and patient tolerance. After the operation, all patients had a standard medication using intravenous (IV) PCA as follows: 5 mg morphine IV bolus at first, followed by 1.2 mg/h, which can be maximally delivered by every patient with a 5–10 min lockout period for the first 48 postoperative hours (POHs). Following, additional dose of morphine or Ketorolac (administered via an intramuscular route at a dose of 15 mg every 6–8 h) were given if the VAS score was >4 [1, 9]. No oral pain killers were administered in the present study.

Surgical technique and wound catheter placement

All patients received a standard muscle-sparing thoracotomy, preserving the latissimus dorsi and serratus anterior muscles. Briefly, after dissection of subcutaneous attachments, the latissimus dorsi was mobilized and retracted posteriorly to expose the serratus anterior muscle; this one was freed from the tip of the scapula and the anterior surface of the sixth rib, and thus retracted forward to gain access to the chest cavity. At the end of the surgical procedure, one chest drain was placed between the 8th and 11th intercostal spaces except in patient undergoing pneumonectomy where no drain was placed. Following the reapproximation of ribs with absorbable sutures, the surgeon inserted a 22.5 cm multiholed catheter, through an introducer needle, from the lower end of the thoracotomy incision. The catheter was sutured in place between the pericostal sutures, as close as possible to the intercostal nerve, and the deep surface of the serratus muscle along its full length. The tip was located within periscapular space, where

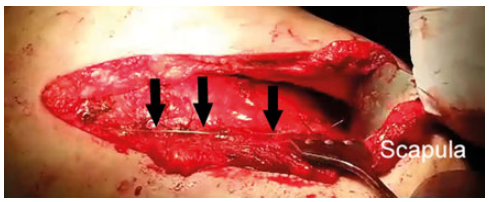

Figure 1: The wound catheter (black arrows) was placed between the pericostal sutures and the deep facet of the serratus muscle for its entire length; the tip of catheter was located within the periscapular space.

the serratus was freed from the scapula (Fig. 1). After skin closure, the catheter was secured with sterile tape. The extrathoracic end of the catheter was connected to an elastomeric pump that contained a flow regulator, which allowed a 2 mg/ml bupivacaine delivery at a constant flow rate of 2 ml/h for 48 h. An induction dose of 5 ml bupivacaine 2 mg/ml was administered before the patient woke up. For the placebo group, the wound analgesia was carried out with the administration of saline solution using the same procedure of the wound Group.

According to previous experiences [10–14], we planned to remove the catheter in both groups 48 h after the operation or earlier in case of side-effects.

Inter-groups differences assessment criteria

Cytokines. Blood samples were collected from an antecubital vein in intervals: before surgery, at 6, 12, 24, 48 and 72 postoperative hours (POHs). The sample has been kept in the test tube for 30 min for clotting; after that it was centrifugated at 3000 G for 5 min and then stored in deep refrigeration at −80°C until serum cytokine measurements (pg/ml). IL-6, IL-10 and tumour necrosis factor-alpha (TNF-alpha) were measured by the same technician using commercially available enzyme-linked immunosorbent assay. The technician was blinded to patient group allocations.

Pain. The VAS, divided in 11 units from 0 (no pain) to 10 (worst pain imaginable) was administered to all patients at 6, 12, 24, 48, 72, 96 and 120 POHs at rest and after coughing. Briefly, patients had to touch a point corresponding to their grade of pain, and this mark indicated the pain level on the scale.

Respiratory function. Pulmonary functional test of FVC% and FEV 1% were measured before and at 72, 96 and 120 POHs using Spirolab III, Spirometer (Cosmed®). The best of three efforts was used for the analysis.

Analgesic requirement. The additional intake of morphine and additional analgesics (Ketorolac) have been recorded for each patient from the operation up to 48 POHs [0–6 (T1); 6–12 (T2); 12–18 (T3); 18–24 (T4); 24–30 (T5); 30–36 (T6); 36–42 (T7) and 42–48 (T8) POHs]. Side-effects as nausea, vomiting, respiratory depression, sedation and pruritus were reported and treated with appropriate medication.

Bupivacaine concentrations. We examined venous blood samples at 6, 12, 18, 24, 30, 36, 42 and 48 POHs. The plasma concentration of bupivacaine was measured using high-performance liquid chromatography as described elsewhere [15]. The maximum concentration (Cp_{max}) and the time to reach Cp_{max} (T_{max}) for bupivacaine in individual patients were assessed directly from the measured values. We calculated the area under the plasma concentration–time curvefor each patient with the trapezoidal rule (NCSS for Windows 1999; NCSS, Kaysville, UT, USA).

Statistical analysis

Results are reported as means ± standard deviations (SDs) for continuous variables and as percentages for categorical variables. According to previous studies [9, 10], a sample size of at least 20 patients per group was required to detect a 20% difference of VAS scores between the control and the wound group with a statistical power of 0.80 and a two-tailed alpha of 0.05. Inter-group differences were assessed using the χ^2 test and the Mann–Whitney test, as appropriate. The inter-group difference between the variables measured at the various postoperative time points was achieved by repeated measures analysis of variance (ANOVA test) and, if appropriate, corrected with the Bonferroni *post hoc* test. A value of $P < 0.05$ was considered statistically significant. The MedCalc® statistical software (Version 12.3, Broekstraat 52; 9030 Mariakerke; Belgium) was used for analysis.

RESULTS

In the wound group, 3/30 patients were excluded because of consent withdrawal ($n = 1$) and lack of cytokine level measurement ($n = 2$). In the placebo group, 2/30 patients were excluded because of consent withdrawal ($n = 1$) and lack of cytokine level measurement ($n = 1$). Thus, the wound group and the placebo group counted 27 and 28 patients, respectively. A study flow diagram according to CONSORT guidelines [16] was reported in Fig. 2.

The two study groups were well matched regarding preoperative data including age, sex, Charlson comorbidity score, clinical stage and preoperative spirometric values. In addition, no significant differences were found on postoperative data including length of skin incision, type of resection, operation time, transfusions, length of chest drainage, hospital stay and postoperative complications. The characteristics of the two study groups are summarized in Table 1.

Cytokines

Table 2 shows the different levels of IL-6, IL 10 and TNF-alpha among the two study groups before and at different time points of the postoperative course. The IL-6 ($P < 0.001$, Fig. 3A), IL-10 ($P < 0.001$, Fig. 3B) and TNF-alpha ($P < 0.001$, Fig. 3C) levels were significantly lower in the wound group than in the placebo group during the entire postoperative course but they were similar before operation.

Pain

Table 2 summarizes the subjective pain scores of the LA and placebo groups during the postoperative course. The VAS scores of the wound group was significantly lower than those of the placebo group at rest ($P < 0.001$, Fig. 4A) and after coughing ($P = 0.01$; Fig. 4B).

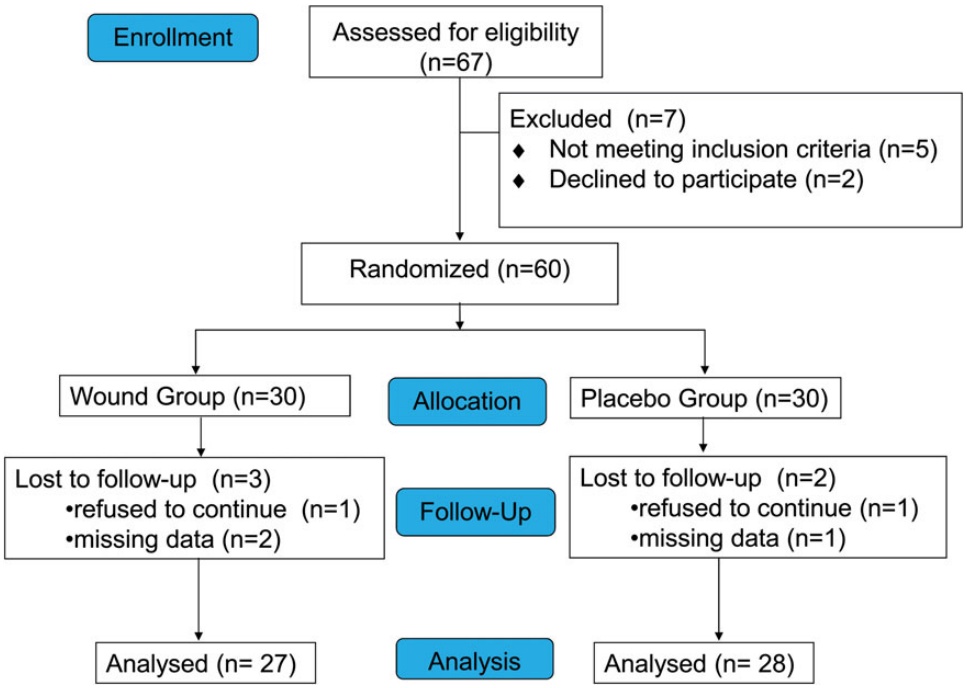

Figure 2: Flow chart of the study according to CONSORT guidelines [16].

Table 1: Characteristics of study population

Variables	Total	Wound group	Placebo group	*P*-values
Number of patients	55	27	28	
Male (%)	32 (58%)	17 (63%)	15 (53%)	0.7
Age (years)	63 ± 2.4	63 ± 1.5	62 ± 7.1	0.8
Charlson comorbidity index	1.4 ± 3.1	1.4 ± 2.8	1.4 ± 5.8	0.6
Clinical stage				
Ia	3 (5%)	2 (7%)	1 (3%)	0.6
Ib	16 (29%)	7 (26%)	9 (32%)	0.7
IIa	18 (33%)	8 (30%)	10 (36%)	0.7
IIb	18 (33%)	10 (37%)	8 (29%)	0.7
FEV1%	81 ± 8.5	79.9 ± 9.3	82.9 ± 7.5	0.3
FVC%	84.6 ± 6	83.1 ± 6.5	86 ± 5.1	0.1
Type of resection				
Segmentectomy	1 (2%)	1 (4%)	0	1.0
Lobectomy	52 (96%)	25 (92%)	27 (97%)	0.7
Bilobectomy	2 (2%)	1 (4%)	1 (3%)	0.4
Histology				
Adenocarcinoma	29 (53%)	14 (52%)	15 (54%)	0.7
Squamous cell carcinoma	23 (42%)	11 (41%)	12 (43%)	1.0
Large cell carcinoma	3 (5%)	2 (7%)	1 (3%)	0.6
Pathological stage				
Ia	2 (4%)	1 (4%)	1 (3%)	0.4
Ib	13 (23%)	6 (22%)	7 (25%)	0.7
IIa	16 (29%)	7 (26%)	9 (33%)	0.7
IIb	22 (40%)	12 (44%)	10 (36%)	0.7
IIIA	2 (4%)	1 (4%)	1 (3%)	0.4
Length of skin incision (cm)	6.5 ± 2.3	6.6 ± 4.5	6.5 ± 6.5	0.9
Operative time (min)	169 ± 12.3	170 ± 6.8	168 ± 4.8	0.8
Blood transfusion (no. patients)	5 (12%)	3 (15%)	2 (10%)	0.6
Chest drain length (days)	5.7 ± 3.6	5.6 ± 1.6	5.9 ± 6.7	0.4
Hospital stay (days)	7.2 ± 4.9	7.0 ± 2.9	7.5 ± 3.9	0.6
Postoperative complications				
Atelectasis	3 (5%)	1 (4%)	2 (7%)	1.0
Air leaks	2 (4%)	1 (4%)	1 (3%)	0.4
Atrial fibrillation	1 (2%)	0	1 (3%)	1.0

Data are expressed as means±standard deviations (SDs) and/or as percentages. *P*-value was calculated using the χ^2 test and the Mann–Whitney test.
FEV1%: forced expiratory volume in 1 s; FVC: forced vital capacity; no: number.

Table 2: Variables measured before and at different time points of the postoperative course

Data	Groups	Before surgery	6 POHs	12 POHs	24 POHs	48 POHs	72 POHs	96 POHs	120 POHs
IL-6	Wound	3.9 ± 2.8	248 ± 10	154 ± 15	105 ± 17	82 ± 17	48 ± 12	–	–
	Placebo	4.0 ± 2.1	441 ± 93	331 ± 70	257 ± 36	175 ± 36	128 ± 25	–	–
IL-10	LA	35.8 ± 13	199 ± 24	131 ± 21	91 ± 10	80 ± 7.8	72 ± 6.5	–	–
	Placebo	32 ± 17	259 ± 43	210 ± 49	168 ± 36	143 ± 30	138 ± 25	–	–
TNF-alpha	Wound	64 ± 6.7	852 ± 80	613 ± 140	432 ± 176	298 ± 137	241 ± 106	–	–
	Placebo	67 ± 12	914 ± 127	767 ± 96	676 ± 82	574 ± 104	468 ± 102	–	–
VAS at rest	Wound	–	7.2 ± 0.8	6.0 ± 0.6	5.1 ± 0.7	4.7 ± 0.7	4.7 ± 0.8	4.3 ± 0.6	3.4 ± 07
	Placebo	–	7.3 ± 0.6	6.2 ± 0.6	6.0 ± 0.7	5.9 ± 0.6	5.3 ± 0.4	5.1 ± 0.3	4.0 ± 0.5
VAS after coughing	Wound	–	7.5 ± 0.6	6.8 ± 0.9	6.5 ± 0.8	5.9 ± 0.7	5.5 ± 0.5	5.2 ± 0.5	4.0 ± 0.6
	Placebo	–	7.6 ± 0.4	6.9 ± 0.6	6.6 ± 0.7	6.3 ± 0.7	5.8 ± 0.7	5.5 ± 0.5	4.2 ± 0.4
FEV1%	Wound	79.9 ± 9.3	–	–	–	–	63.6 ± 65.2	67 ± 5.9	69.7 ± 5.7
	Placebo	82.9 ± 7.5					55.8 ± 6.9	57.2 ± 6.6	65 ± 6.0
FVC%	Wound	83.1 ± 6.5	–	–	–	–	63 ± 7.4	71.2 ± 5.0	71.5 ± 6.5
	Placebo	86 ± 5.1	–	–	–	–	57.9 ± 5.9	65.3 ± 4.8	68.2 ± 3.8

Data are expressed as means±standard deviations (SDs).
VAS: visual analogue scale; POHs: postoperative hours; TNF-alpha: tumour necrosis factor-alpha.

Respiratory function

Table 2 reports the FVC% and FEV1% mean values among the different study groups. The wound group had a faster recovery of FEV1% ($P = 0.01$; Fig. 5A) and of FVC% ($P = 0.02$; Fig. 5B) than the placebo group.

Analgesic requirement

The wound compared with the placebo group required a lower level of additional morphine injection at T1 (2.6 ± 0.5 vs 2.7 ± 0.4); T2 (3.3 ± 0.5 vs 3.4 ± 0.4); T3 (3.2 ± 0.4 vs 3.5 ± 0.4); T4 (3.1 ± 0.7 vs 3.4 ± 0.3); T5 (2.9 ± 0.6 vs 3.2 ± 0.3); T6 (2. ± 0.4 vs 3.1 ± 0.3); T7 (2.4 ± 0.5 vs 2.8 ± 0.3) and T8 (1.7 ± 0.6 vs 2.1 ± 0.4) postoperative time. The repeated measures with the ANOVA test in the two study groups have a *P*-value of 0.03 (Fig. 6A). Also a significant reduction of total Ketorolac consumption was observed in the wound group compared with the placebo group (14.5 ± 15.8 vs 26.4 ± 11.4; $P = 0.01$).

Bupivacaine blood concentration

Bupivacaine serum concentration continued to rise with continuous instillation until the end of instillation (Fig. 6B). Nevertheless, in the wound group patients it was <4 μg/ml at the end of 48 POHs. Besides, no local complications related to the catheter including wound infection, postoperative haematoma, cellulitis, necrosis and foreign body reaction were reported in all our patients.

DISCUSSION

Thoracotomy pain is among the most severe kinds of pain for patients and its treatment is very challenging for clinicians. A myriad of techniques have been used for postoperative pain control, from patient-controlled IV opioids, epidural analgesia to surgically placed inter-costal blocks and paravertebral blocks, but no method is both effective and devoid of side-effects. In recent years, there has been a resurgence of interest in using continuous administration of LAs to create a regional field block at the level of the surgical wound. Several studies [6–8] have shown that wound analgesia results in a significant decrease in pain scores and narcotic use after gynaecological, urological, intestinal, orthopaedic, plastic and cardiac surgery. In thoracic surgery, a wound catheter is placed in a variety of peripleural locations including extrapleural, inter-pleural and intrapleural but, surprisingly, in only a few studies [10–14, 17] it has been placed within subcutaneous or deeper spaces to administer LAs, probably to prevent potential side-effects such as local infection, haematoma and delayed wound healing or toxic systemic effects.

Our results demonstrate that wound analgesia provides an adequate significant pain control with reduction of cytokine levels, pain score and opioid intake and a faster restoration of spirometric values, confirming its effectiveness in pain relief. The two study groups did not have any significant difference regarding preoperative data including Charlson comorbidity index and respiratory function. The resection was performed by the same surgeon through a standard muscle-sparing thoracotomy; the type of resection and operative time were similar between the two groups; so also were other factors that may influence the inflammatory reaction and thus the cytokine levels including length of skin incision, transfusions and postoperative complications.

Direct application of LAs in the surgical field could provide analgesia through a direct and indirect mechanism. Bupivacaine directly acts on the local nerves, injured by thoracotomy and inhibits membrane depolarization by interfering with Na^+ currents; this prevents the propagation of the pain neuronal signal to the spinal cord. However, surgical trauma also favours the local inflammatory reaction and the release of biological pain mediators that coregulate the transmission of nociceptive stimuli from the periphery (injured tissue) to the central nervous system. Thus, the anti-inflammatory effect due to reduction of inflammatory mediators such as IL-6, IL-10 and TNF-alpha also reduces the sensitization of nociceptive receptors and contributes to pain relief and hypoalgesia. This results in a significant reduction of the pain score and a better respiratory function recovery in the wound group than in the placebo group, findings that need to be discussed from different aspects.

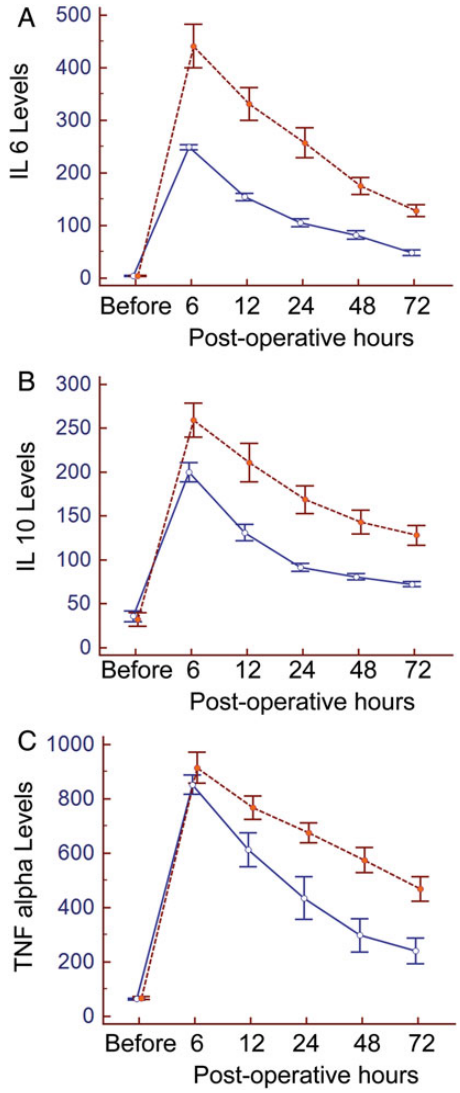

Figure 3: The levels of IL 6 [$P < 0.001$, Part (**A**)], IL 10 [$P < 0.001$, (**B**)] and TNF-alpha [$P < 0.001$, (**C**)] are significantly lower in the wound group (empty circle) than in the placebo group (full circle) during the entire postoperative course.

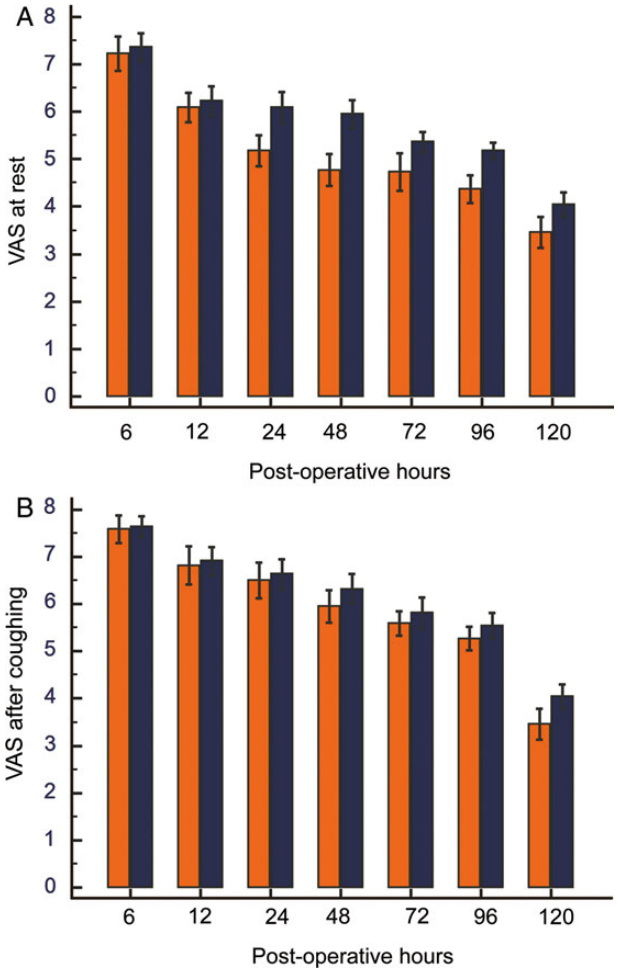

Figure 4: The VAS scores of the wound group (orange bars) are significantly lower than those of the placebo group (blue bars) at rest [$P < 0.001$; (**A**)] and after coughing [$P = 0.01$; (**B**)].

First of all, the reduction of VAS scores is more evident 12 h after the operation despite the infusion of LA starting immediately after operation, probably because the residual anesthetics administered during the operation still influenced the pain perception during the immediate postoperative time.

Moreover, the beneficial effects of wound analgesia were significant also 48 h after the operation, despite catheter removal. Probably, the continuous infusion of bupivacaine prolongs the reduction of peripheral nerve sensitization and prevents the propagation of nerve pain stimuli to the spinal cord. Similarly, studies in animals have shown that parietal pain may sensitize spinal cord neurons to visceral colic pain, and these data suggest that the afferent nerve impulse block may reduce spinal dorsal horn neuron sensitization, consequently providing analgesia over the duration of wound infusion [18]. Although the difference is not statistically significant, the placebo group presents a slightly longer chest drain time than the wound group. Thus, the fraction of tube-bearing patients in the placebo group exceeds the fraction in the wound group at most of the set time points and it could additionally explain the ongoing positive effects of wound analgesia also after catheter removal.

In addition, in the wound group, there is a significant recovery of FEV1, which reached ~90% of the estimated post-resectional value on the FEV1 after 5 postoperative days. After lung resection with lobectomy, FEV1 decrease is usually caused not only by the lung parenchyma resection but also by impairment of the diaphragm and chest wall motility, leading to an increase in pulmonary residual volume. Thus, we speculate that the reduction in inflammatory response at the level of surgical trauma could favour chest wall motility and facilitate the early recovery of respiratory function. In addition, wound group patients did not have any significant respiratory complications such as air leaks or atelectasis that prevented complete lung expansion and thus experienced recovery of respiratory function. This could also explain why chest drainage removal was faster in the wound than in the placebo group, as reported above. Recent papers have reported that FEV1 was 30% lower than the predictive preoperative value in the early postoperative days and improved in the following days [19]. It is unclear whether wound analgesia can improve respiratory function also in the first days of the postoperative course since we started to register spirometric values only 3 days after operation.

Despite the significant reduction of VAS scores in the active control group, the VAS value was >5 at 24 postoperative hours,

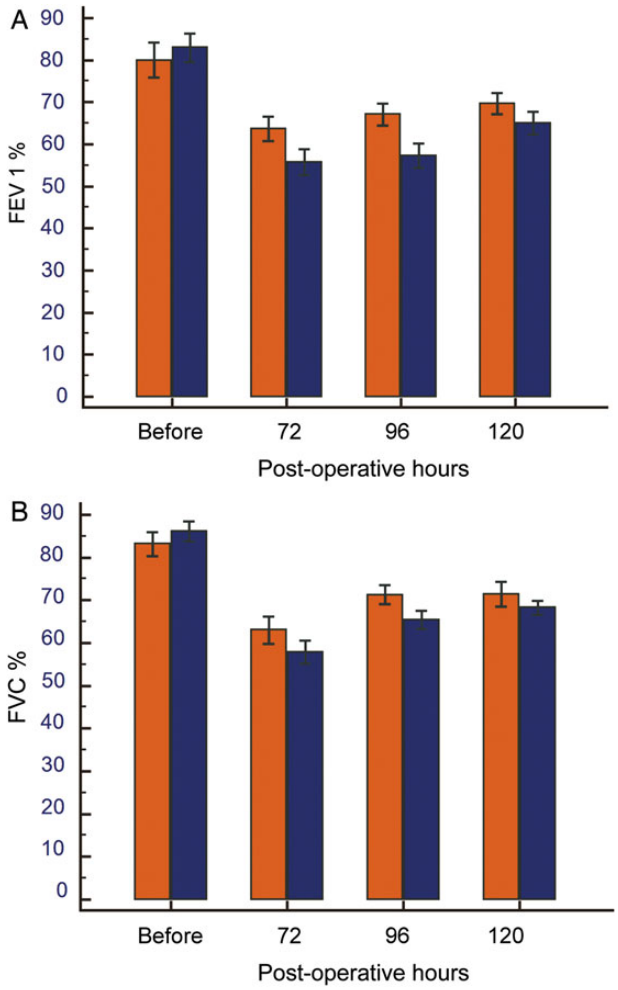

Figure 5: The wound group (orange bars) presented a faster recovery of FEV1% [$P = 0.01$; (**A**)] and of FVC% [$P = 0.02$; (**B**)] than the placebo group (blue bars).

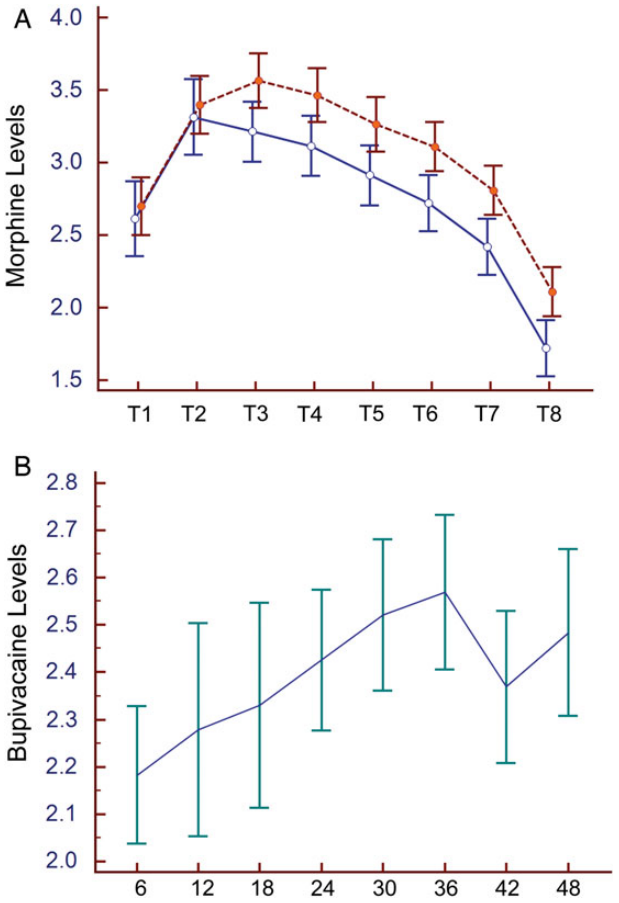

Figure 6: The wound group (empty circle) compared with the placebo group (full circle) shows significantly lower levels of additional morphine injection (μg/ml) ($P = 0.03$) (**A**). T1: 0–6 POHs; T2: 6–12 POHs; T3: 12–18 POHs; T4: 18–24 POHs; T5: 24–30 POHs; T6: 30–36 POHs; T7: 36–42 POHs and T8: 42–48 POHs. The serum concentration of bupivacaine continued to rise with continuous instillation until the termination of instillation, but it was < 4 μg/ml (toxic level) at the end of 48 POHs (**B**). POHs: postoperative hours. FVC%: forced vital capacity; FEV1%: flow expiratory volume in 1 s.

probably because we usually give additional pain killers if the VAS value was >4, in agreement with other reports [1, 9].

Previous studies [10, 11, 13, 14, 17] have reported both different types of LA (bupivacaine or lidocaine), different injection techniques (intermittent bolus versus continuous bolus) and change in the number of wound catheters for analgesia after thoracotomy.

We preferred to use bupivacaine rather than lidocaine considering its longer action (4 h versus 2, respectively). Nevertheless, repeated administration to preserve an adequate analgesia for more than 6 h was required. To overcome this limitation, we used a disposable elastomeric continuous infusion pump as an alternative to repeated boluses. Kristek *et al*. [14] found that wound analgesia in 11 of 49 patients was unable to have an efficient control of post-thoracotomy pain and a supplemental IV analgesic was required probably because bupivacaine was administered with a bolus twice a day rather than with a continuous infusion. In our cases, the continuous infusion has provided efficient pain relief for the entire postoperative course without any risk of systemic toxicity, considering that the bupivacaine plasma levels have remained consistently far below the established toxic threshold (4 μg/ml) [13]. Despite this, the reduction of the VAS score was more evident at rest than after coughing. Probably during coughing patients may need a supplemental dose of LAs; a continuous infusion pump does not allow in-process dose adjustment.

In all previous studies [10, 11, 13, 14, 17], the authors have placed two wound catheters for wound analgesia, one close to the pericostal sutures and another above the fascia in the subcutaneous space. In our study, all patients received a muscle-sparing thoracotomy, a technique that preserves the latissimus dorsi and serratus anterior muscles. Supposing that the most painful procedure manoeuvre is the dissection of the serratus muscle, we inserted only one catheter between the pericostal sutures and the deep surface of the serratus muscle for its entire length. The administration of bupivacaine at this level reduces the afferent painful stimuli generated from the inter-costal nerve and from the damaged muscular and ligamentous structures in the periscapular region. Thus, the position of the catheter is crucial for the effectiveness of wound analgesia. After thoracic surgical procedures, when the catheter was placed in the subcutaneous tissue, only a discrete reduction of pain was observed, while more positive results were obtained with deeper placement of the catheters [20]. Catheters placed above the fascia were found to provide ineffective analgesia, whereas catheters placed in the preperitoneal layer have been shown to reduce postoperative pain and accelerate recovery after colorectal surgery [21, 22]. Additionally, the study performed by Wu *et al*. [23] after prostatectomy illustrates the need for deep placement of the wound catheter.

The use of one catheter compared with the use of two has had similar clinical effects on pain relief, but in theory one could have reduced the local inflammatory response, the risk of infection and of toxic accumulation of LAs with two different infusion pumps.

As reported above, epidural analgesia is considered the gold standard strategy for thoracotomy pain relief. However, the difficulty of placing the epidural catheter in patients with anatomical abnormalities, the presence of patient comorbidities (coagulopathy and haematological abnormalities) and the potential complications related to epidural analgesia (hypotension, urinary retention, pruritus and neurological damage) limit its use in clinical practice.

Alternatively, several authors have reported that inter-costal and/or paravertebral block have similar efficacy to epidural analgesia in terms of the quality of the analgesia. However, such strategies require the formation of an extrapleural pocket for placing the catheter [24] and cannot be applied after surgical procedures such as pleurectomy and/or chest wall resection. In addition, unfavourable factors such as pleural adhesion may preclude proper access to the posterior inter-costal spaces and tear parietal pleura, allowing LA leakage from the injection site with potential analgesic failure.

On the other hand, the insertion of a wound catheter is a simple procedure that does not require particular manoeuvres by the surgeon such as the peeling of parietal pleura. There is no diffusion barrier for the LA to overcome. In addition, LA has direct access to the inter-costal nerves without being diluted by fluids in the pleural cavity. Unlike continuous epidurals, which require maintenance, titration and management of complications, the elastomeric infusion pump does not require any adjustment or care by physicians or the nursing staff after operation. No complications including wound infection, postoperative haematoma, cellulitis, necrosis, reaction to the foreign body or drug toxicity were registered in all our patients, which confirmed that it is also a safe procedure, in agreement with other experiences [10, 11, 13, 14, 17]. The only contraindication to its use is the allergy to LAs. Thus, wound analgesia may be an attractive alternative especially for such groups of patients where other strategies are not indicated for particular anatomical conditions and/or the presence of comorbidities.

STUDY LIMITATIONS

Our study presents several limitations as follows.

(i) We placed a catheter in all patients, and so no comparison with a non-catheter group can be made.

(ii) A PCA pump was not applied to the wound catheter and that may limit the control of pain after coughing, as reported above. Because all patients received IV PCA analgesia, we avoided using another PCA that could generate confusion in the patients.

(iii) All patients received IV PCA analgesia in addition to wound analgesia. Thus, our study design was unable to demonstrate if wound analgesia alone could be an efficacious procedure to control post-thoracotomy pain. However, wound analgesia is unable to intercept all components of post-thoracotomy pain: unblocked pain impulses may arise from diaphragmatic pleura, which is innervated by the vagus nerve; from the mediastinum, which is innervated by the vagus nerve; and from incision in the skin, which is innervated by cutaneous nociceptive nerves [25].
   (a) Thus, an additional analgesic procedure is mandatory in line with modern analgesia strategies, which suggests a combination of different techniques and drugs to optimize control of postoperative pain.
   (b) Multiple studies with regional anaesthesia strategies in combination with systemic analgesics have demonstrated improved patient outcomes and lower opioid consumption [12], as observed in our wound group, therefore avoiding or decreasing opioid adverse effects (nausea, vomiting, suppression of respiratory reflexes and hypoventilation) and making more tolerable IV analgesia, especially in patients in whom systemic opioids are best minimized.

(iv) A slightly longer and far more variable chest drain time was observed for the control group that could infer with the set time points for measurements.

CONCLUSIONS

Our study demonstrates that wound analgesia associated with IV PCA is an effective, easy and safe procedure for post- thoracotomy pain control. The local administration of bupivacaine with a catheter inserted between the pericostal sutures and the serratus muscle reduces the nerve pain transmission through a direct (blocking the Na^+ channels of the injured nerve) and indirect mechanism (reduction of cytokine release). The clinical benefits are the reduction of pain scores and opioid requirement, and a faster respiratory function recovery. Thus, our current practice is to use such a strategy in patients undergoing muscle-sparing thoracotomy and we hope that it will gain widespread use also in other centres.

Conflict of interest: none declared.

REFERENCES

[1] Fiorelli A, Morgillo F, Milione R, Pace MC, Passavanti MB, Laperuta P *et al*. Control of post-thoracotomy pain by transcutaneous electrical nerve stimulation: effect on serum cytokine levels, visual analogue scale, pulmonary function and medication. Eur J Cardiothorac Surg 2012;41:861–8.
[2] Soto RG, Fu ES. Acute pain management for patients undergoing thoracotomy. Ann Thorac Surg 2003;75:1349–57.
[3] Salomaki TE, Laitinen JO, Nuutinen LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after thoracotomy. Anesthesiology 1991;75:790–5.
[4] Benzon HT, Wong HY, Belavic AM Jr, Goodman I, Mitchell D, Lefheit T *et al*. A randomized double-blind comparison of epidural fentanyl infusion versus patient-controlled analgesia with morphine for postthoracotomy pain. Anesth Analg 1993;76:316–22.
[5] Grant RP, Dolman JF, Harper JA, White SA, Parsons DG, Evans KG *et al*. Patient-controlled lumbar epidural fentanyl compared with patient-controlled intravenous fentanyl for post-thoracotomy pain. Can J Anaesth 1992;39:214–9.
[6] Grant RP, Dolman JF, Harper JA, White SA, Parsons DG, Evans KG *et al*. Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. J Am Coll Surg 2006;203:914–32.
[7] Merritt CK, Mariano ER, Kaye AD, Lissauer J, Mancuso K, Prabhakar A *et al*. Peripheral nerve catheters and local anesthetic infiltration in perioperative analgesia. Best Pract Res Clin Anaesthesiol 2014;28:41–57.
[8] Ventham NT, Hughes M, O'Neill S, Johns N, Brady RR, Wigmore SJ. Systematic review and meta-analysis of continuous local anaesthetic wound infiltration versus epidural analgesia for postoperative pain following abdominal surgery. Br J Surg 2013;100:1280–9.

[9] Fiorelli A, Vicidomini G, Laperuta P, Busiello L, Perrone A, Napolitano F *et al*. Pre-emptive local analgesia in video-assisted thoracic surgery sympathectomy. Eur J Cardiothorac Surg 2010;37:588–93.
[10] de Almeida MC, de Figueiredo Locks G, Gomes HP, Brunharo GM, Kauling AL. Postoperative analgesia: comparing continuous epidural catheter infusion of local anesthetic and opioid and continuous wound catheter infusion of local anesthetic. Rev Bras Anestesiol 2011;61:293–303.
[11] Garutti I, González-Aragoneses F, Biencinto MT, Novoa E, Simón C, Moreno N *et al*. Thoracic paravertebral block after thoracotomy: comparison of three different approaches. Eur J Cardiothorac Surg 2009;35:829–32.
[12] Dowling R, Thielmeier K, Ghaly A, Barber D, Boice T, Dine A. Improved pain control after cardiac surgery: results of a randomized, double-blind, clinical trial. J Thorac Cardiovasc Surg 2003;126:1271–8.
[13] Fortier S, Hanna HA, Bernard A, Girard C. Comparison between systemic analgesia, continuous wound catheter analgesia and continuous thoracic paravertebral block: a randomised, controlled trial of postthoracotomy pain management. Eur J Anaesthesiol 2012;29:524–30.
[14] Kristek J, Kvolik S, Sakić K, Has B, Prlić L. Intercostal catheter analgesia is more efficient vs. intercostal nerve blockade for post-thoracotomy pain relief. Coll Antropol 2007;31:561–6.
[15] Chan SK, Lai PB, Li PT, Wong J, Karmakar MK, Lee KF *et al*. The analgesic efficacy of continuous wound instillation with ropivacaine after open hepatic surgery. Anaesthesia 2010;65:1180–6.
[16] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152:726–32.
[17] Wheatley GH 3rd, Rosenbaum DH, Paul MC, Dine AP, Wait MA, Meyer DM *et al*. Improved pain management outcomes with continuous infusion of a local anesthetic after thoracotomy. J Thorac Cardiovasc Surg 2005; 130:464–8.
[18] Forastiere E, Sofra M, Giannarelli D, Fabrizi L, Simone G. Effectiveness of continuous wound infusion of 0.5% ropivacaine by On-Q pain relief system for postoperative pain management after open nephrectomy. Br J Anaesth 2008;101:841–7.
[19] Ercegovac M, Subotic D, Zugic V, Jakovic R, Moskovljevic D, Bascarevic S *et al*. Postoperative complications do not influence the pattern of early lung function recovery after lung resection for lung cancer in patients at risk. J Cardiothorac Surg 2014;9:92.
[20] Wu CL, Cohen SR, Richman JM, Rowlingson AJ, Courpas GE, Cheung K *et al*. Efficacy of postoperative patient-controlled and continuous infusion epidural analgesia versus intravenous patient-controlled analgesia with opioids: a meta-analysis. Anesthesiology 2005;103:1079–88.
[21] Fredman B, Zohar E, Tarabykin A, Shapiro A, Mayo A, Klein E *et al*. Bupivacaine wound instillation via an electronic patient-controlled analgesia device and a double-catheter system does not decrease postoperative pain or opioid requirements after major abdominal surgery. Anesth Analg 2001;92:189–93.
[22] Beaussier M, El'Ayoubi H, Schiffer E, Rollin M, Parc Y, Mazoit JX *et al*. Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery: a randomized, double-blind, placebo-controlled study. Anesthesiology 2007;107: 461–8.
[23] Wu CL, Partin AW, Rowlingson AJ, Kalish MA, Walsh PC, Fleisher LA. Efficacy of continuous local anesthetic infusion for postoperative pain after radical retropubic prostatectomy. Urology 2005;66:366–70.
[24] Sabanathan S, Richardson J, Mearns AJ. Efficacy of continuous intercostal bupivacaine for pain relief after thoracotomy. Br J Anaesth 1993;71:463–4.
[25] Chan VW, Chung F, Cheng DC, Seyone C, Chung A, Kirby TJ. Analgesic and pulmonary effects of continuous intercostal nerve block following thoracotomy. Can J Anaesth 1991;38:733–9.