ORIGINAL ARTICLE

THORACIC

Preventive analgesia in thoracic surgery: controlled, randomized, double-blinded study[†]

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Abstract

OBJECTIVES: Preventive analgesia is defined as a treatment that is commenced before the surgical procedure in order to diminish the physiological consequences of afferent nociceptive transmission caused by the procedure and prevent central sensitization. The analysis of randomized studies of preventive analgesia is controversial. The aim of this study was to check the analgesic efficacy of preoperative administration of dextromethorphan associated with intercostal nerve block with levobupivacaine in thoracotomy patients who refused or had a contraindication to epidural analgesia.

METHODS: This study was a four-arm, double-blinded, randomized placebo-controlled trial. Patients were allocated following close block randomization into four arms: 'Group A' preoperative dextromethorphan and preoperative intercostal block (IB), 'Group B' preoperative placebo and preoperative IB, 'Group C' preoperative dextromethorphan and postoperative IB, 'Group D' preoperative placebo and postoperative block. The primary end-point was the cumulative morphine consumption (CMC) within the first 14 days after surgery.

RESULTS: A total of 400 patients were enrolled and 395 completed the study. There were no statistical differences among the groups in terms of demographic and surgical data; in contrast, preoperative quality-of-life scores were heterogeneous. The mean CMCs were as follows: Group A 111.4 mg, Group B 121.5 mg, Group C 126.8 mg, Group D 138.3 mg. Group A mean was lower than the maximum ($P = 0.0001$). The CMC value did not correlate with age, sex, body mass index, education, type of surgery, length or width of the incision and rib fracture. Postoperative functional data and post-thoracotomy syndrome prevalence were homogeneous; female gender resulted predictive for post-thoracotomy syndrome.

CONCLUSIONS: Results indicate that preoperative administration of dextromethorphan associated with preoperative IB with levobupivacaine provided preventive analgesia, decreasing analgesic administration during the early postoperative period compared with placebo and/or postoperative IB. This study failed in detecting any effect of preventive analgesia on functional items and post-thoracotomy syndrome.

Keywords: Preventive • Analgesia • Thoracic surgery

INTRODUCTION

It is well known that thoracic surgery is characterized by pain, which is remarkable for its intensity and duration; in addition, thoracotomy is considered to be a procedure that triggers severe chronic postoperative pain [1]. Adequate pain management seems to decrease postoperative complications, to shorten hospital stay and to improve patient rehabilitation [2]. In this perspective, preventive analgesia has become one of the most promising strategies of postoperative pain control [3].

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

Preventive analgesia is defined as a treatment that is commenced before the surgical procedure in order to diminish the physiological consequences of afferent nociceptive transmission caused by the procedure and, consequently, to prevent central sensitization [4, 5]. To be honest, the dispute over the appropriate definition of preventive analgesia has produced a multiplicity of dissimilar designations (such as pre-emptive analgesia, balanced periemptive analgesia, protective analgesia and pre-emptive antihyperalgesia); such puzzlement originated from a variety of different treatment combinations that have been used by the researchers [6]. Actually, the analysis of clinical results from randomized, controlled studies of preventive analgesia is controversial and the prevalent opinion is

that no major clinical advantages have been clearly demonstrated [7, 8].

The current randomized, double-blinded, prospective study was designed to check the analgesic efficacy of preoperative administration of dextromethorphan associated with intercostal nerve block with levobupivacaine in thoracotomy patients.

PATIENTS AND METHODS

Study design

This study was a four-arm, double-blinded, randomized placebo-controlled trial comparing preoperative administration of dextromethorphan versus placebo in thoracotomy patients receiving preoperative or postoperative intercostal block (IB) with levobupivacaine. The study protocol was approved by the local Ethical Committee and written informed consent was obtained from all enrolled patients; the study followed the principles of the Declaration of Helsinki. The study setting was 'Fondazione Cà Granda Ospedale Maggiore .Policlinico', the main university hospital in Milan, which is the largest city in the north of Italy. Patients were allocated following close block randomization into four arms: 'Group A' preoperative dextromethorphan and preoperative IB, 'Group B' preoperative placebo and preoperative IB, 'Group C' preoperative dextromethorphan and postoperative IB, 'Group D' preoperative placebo and postoperative IB.

Patient selection

Patient selection included the following: scheduled thoracotomy for pulmonary resection, age from 18 to 75 years old, Easter Cooperative Oncology Group performance status 0-2 and contraindication as well as refusal of epidural analgesia. Exclusion criteria were as follows: surgical procedure including parietal pleura resection or chest wall resection, preoperative thoracic pain, continuous use of analgesics, history of thoracic trauma, history

of thoracic surgery, alcohol or drugs abuse, pregnancy or lactation, insulin-dependent diabetes, polyneuropathy, intolerance to dextromethorphan or levobupivacaine, WBC <4000 μl, platelet <100 000 μl, haemoglobin <8.5 g/dl, creatinine >3.0 mg/dl, arterial carbon dioxide partial pressure (pCO_2) >50 mmHg and postoperative predicted forced expiratory volume in 1 s (FEV_1) <800 ml.

Randomization and intervention

Patients, nursing staff and surgeons were blinded to treatment arms until the conclusion of the study; a resident enrolled the patients, followed the randomization procedure and prepared the drugs and the placebos. A sealed envelop including the specific arm treatment was enclosed to each patient's record for an emergency purpose. Study interventions consisted in per os administration of water (10 ml) containing 1.5 mg/kg of dextromethorphan (Aricodil drops, Menarini, Florence, Italy) 2 h before surgery; the placebo was 10 ml of drinkable water. IB was performed by surgeons injecting percutaneously 3 ml of solution in each intercostal space from T2 to T10 on the operative side 20 minutes before operation and at the end of the surgery; the treatment solution consisted of 30 ml of levobupivacaine (Chirocaine 5 mg/ml, Abbott, Abbott Park, Green Oaks, IL, USA), the placebo was 30 ml saline solution. All patients received general anaesthesia with sodium thiopental (5-7 mg/kg), halogenated hydrocarbon anaesthetic and fentanyl (0.5-1.5 μg/kg). A non-steroidal anti-inflammatory drug was administered at anaesthesia induction (ketorolac 0.4 mg/kg). The standard postoperative pain management consisted in intravenous opioid analgesic administration (morphine 0.014-0.042 mg/kg/h) associated with non-steroidal anti-inflammatory drugs (ketorolac 30 mg i.v. three times a day or acetaminophen 500 mg + codeine 30 mg per os three times a day). Figure 1 shows details of the study design and time schedule.

Surgery procedure included pulmonary resection through standard posterolateral thoracotomy with the division of the latissimus dorsi; two small Finochietto retractors were used to spread
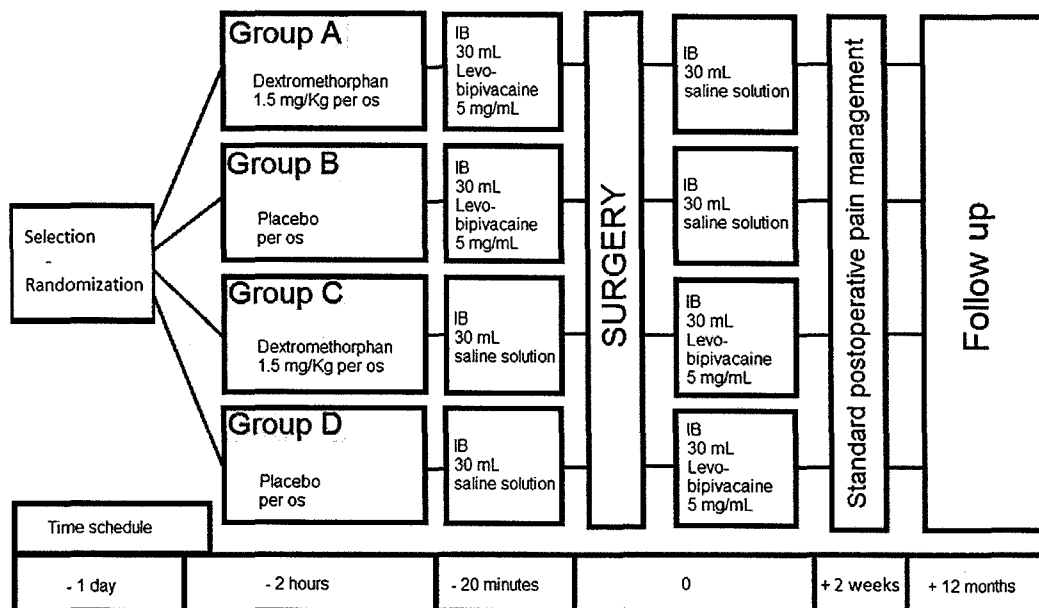

Figure 1: Study design and time schedule.

the ribs. After completion of the pulmonary resection, two chest tubes (Ch 28, Redax, Mirandola, Italy) were positioned and the thoracotomy was sutured with three intercostal stitches, preserving the intercostal pedicle of the caudal rib.

Data collection

The data collection included demographic items and surgical matters (type of surgery, length of the incision, retractor maximum spread, surgery duration and fracture of the ribs). The quantity and type of analgesic drugs delivered were accurately recorded according to the following timetable: daily consumption until the 60th postoperative day, weekly consumption at 3, 6, 9 and 12 months. The pain intensity was recorded with the help of a visual analogue scale (VAS) during rest, during rotation of the homolateral arm as well as during coughing; the tests were obtained the day before operation and at the 2nd, 6th, 12th and 24th postoperative hours. At the 2nd, 3rd, 4th and 5th post-operative day, the mean of the two tests performed during each day was recorded. The VAS was also used during ambulatory visits at 1, 2, 3, 6, 9 and 12 months after surgery. Any discomfort requiring regular analgesic consumption was noted. The heart rate, systemic arterial pressure, respiratory rate and oxygen saturation were recorded following the VAS timetable. Pulmonary function (FEV_1 and oxygen along with carbon dioxide arterial partial pressures) was recorded before operation and daily from the 1st to the 5th postoperative day as well as during the ambulatory visits 1, 2, 3, 6, 9 and 12 months after surgery.

Quality of life was assessed using the EORTC QLQ-C30 (version 3.0), a cancer-specific 30-item core questionnaire, supplemented with the lung-specific module questionnaire: EORTC QLQ-LC13 [9, 10]. Questionnaires were distributed to patients before the operation, and 7 days and 2, 6 and 12 months after surgery. The EORTC QLQ-C30 and LC13 were scored according to the scoring manual and raw scores were linearly transformed in a scale varying from 0 to 100.

The primary end-point was the cumulative morphine consumption (CMC) within the first 14 days after surgery; the analgesics administered were reduced into an equivalent dose of morphine according to the scheme: 520 mg of acetaminophen given orally was considered equivalent to 1 mg of intravenous morphine, codeine:morphine correspondence dose was regarded as 10:1 and ketorolac:morphine correspondence was assumed as 6:1 [11–15].

Secondary end-points were postoperative pain intensity (VAS), pulmonary function, the incidence of chronic pain after thoracotomy (defined as the pain that recurs or persists along a thoracotomy scar at least 2 months following surgical procedure [16]) and quality of life.

Statistical analysis

Descriptive analysis of the study population included means, standard deviations, median and frequencies. The data were analysed with the SAS software JMP 9.0.0 using ANOVA test for qualitative data and x^2 test for all quantitative data. Hsu multiple comparison to the best (MCB) test was used to compare the means that are lesser than the unknown maximum or greater than the unknown minimum. A sample size of 318 patients was estimated based on 80% power, assuming CMC as 100 mg for the best group and increasing 10 points each group; standard deviation was fixed at 60 mg and an α value at 0.05. Finally, it was planned to enrol 400 patients (100 per group) to provide an adequate study population. A value of $P < 0.05$ was considered statistically significant.

RESULTS

The study protocol was proposed to 408 consecutive patients from January 2008 to April 2011; 8 patients declined to participate. Of the 400 patients enrolled, 5 were excluded after surgery: 3 patients needed a reoperation, 2 patients required reintubation and a long stay in the intensive care unit (Fig. 2). All 395 involved patients completed the postoperative pain survey before May 2012. Demographic and surgical data are summarized in Table 1; there were no statistical differences among the groups.

The CMC in the first 14 postoperative days resulted as follows: Group A (mean ± standard deviation) = 111.4 ± 37.2 mg, Group B = 121.5 ± 43.8 mg, Group C = 126.8 ± 47.5 mg, Group D = 138.3 ± 61.3 mg. MCB test identified Group A and B means as significantly lower than the maximum ($P = 0.0001$ and $P = 0.019$, respectively) and Group C and D means as significantly higher than the minimum ($P = 0.032$ and $P = 0.0001$, respectively). Group A CMC was significantly lower than in Groups C and D ($P = 0.025$ and <0.001, respectively) and Group B CMC resulted significantly lower than Group D ($P = 0.014$) when each mean was compared with another. The CMC value did not correlate with age, sex, body mass index, education, type of surgery, length or width of the incision and rib fracture. Table 2 reports the CMC values related to each postoperative day from the 1st to the 5th: Group A means were constantly lower than the maximum and Group D means were always greater than the minimum. The results of the visual analogue scale recorded in the early postoperative period are presented in Table 3. Occasional significant differences among the means were observed. The preoperative and postoperative values of pO_2, pCO_2, FEV_1, respiratory rate and heart rate were homogenous among the groups.

Two months after the surgery, the prevalence of post-thoracotomy pain syndrome was distributed as follows: mild–moderate pain 25.8% (Group A: 24/99 patients, Group B: 26/99, Group C: 23/97 and Group D: 29/100), pain requiring regular analgesic consumption 3%; there were no statistical differences among the groups. Six months after operation, the prevalence of mild-moderate pain decreased to 18.9% (Group A: 15/99 patients, Group B: 21/99, Group C: 17/97 and Group D: 22/100) and analgesic consumption to 2%; 1 year after surgery, the prevalence of mild–moderate pain was 17.9% (Group A: 14/99 patients, Group B: 19/99, Group C: 17/97 and Group D: 19/100) while the analgesic consumption still remained at 2%. Statistical analysis failed to find any differences among the groups; the female gender was the only predictor for post-thoracotomy pain syndrome ($P < 0.001$).

The cohort health-related quality-of-life scores, expressed as mean, were 72.1 before operation, 57.8 7 days after surgery, 68.4 2 months after surgery, 79.5 6 months after surgery and 81.0 12 months after surgery. Excluding the 2 months score, the postoperative values were significantly different from the preoperative score. Preoperative health-related quality-of-life scores were stratified by the groups obtaining the following results: Group A (mean) = 69.6, Group B = 78.8, Group C = 61.5 and Group D = 74.0. Group B and Group D scores were significantly higher than the minimum value.
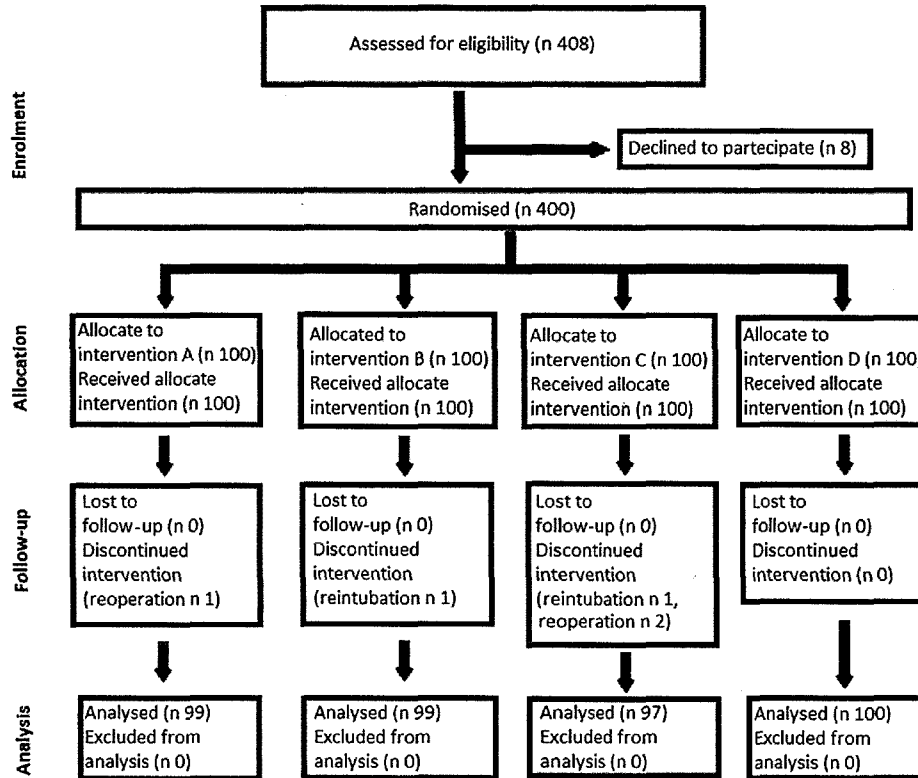
Figure 2: Patients' flow diagram.

Table 1: Demographic and surgical data

	Group A	Group B	Group C	Group D
Number of patients	99	99	97	100
Age (years)	59.0 ± 11.1	60.1 ± 11.1	61.5 ± 10.2	57.2 ± 13.5
Male/female	54/45	56/43	58/39	61/39
BMI	24.6 ± 3.5	25.0 ± 2.8	24.6 ± 3.6	24.2 ± 3.5
Education: a/b/c/d	20/25/37/17	16/27/42/14	25/21/36/15	17/24/39/20
Surgery: e/f/g	32/59/8	27/71/1	39/52/6	40/55/5
Operative time (min)	156.4 ± 62.4	161.1 ± 52.3	154.8 ± 51.0	157.0 ± 60.6
Incision length (cm)	14.5 ± 4.0	14.6 ± 4.3	15.4 ± 3.9	14.8 ± 4.6
Retractor width (cm)	7.0 ± 1.7	6.7 ± 1.7	7.2 ± 1.6	6.6 ± 1.5
Rib fracture, yes/no	16/83	13/86	19/78	17/83

Continuous data are expressed as mean $\pm$ standard deviation.

BMI: body mass index; a: primary school; b: middle school; c: upper school; d: university; e: atypical pulmonary resection; f: pulmonary lobectomy or bilobectomy; g: pneumonectomy.

DISCUSSION

The results of the current randomized, double-blinded, prospective study indicate that preoperative administration of dextromethorphan associated with preoperative IB with levobupivacaine provided preventive analgesia, decreasing analgesic administration (CMC) during the early postoperative period compared with placebo and/or postoperative IB. The CMC in the first 14 days after surgery resulted lower in the Group A versus the other groups (statistical significance versus Groups C and D, tendency versus Group B) supporting the hypothesis that preoperative administration of dextromethorphan could reduce the central hypersensitivity acting as an N-methyl-D-aspartate antagonist [17] when associated with preoperative IB. Considering that central neurons become hyperexcitable after local injury, giving an overstated response to harmless sensory inputs, our result supports the hypothesis that the preoperative administration of local analgesic could reduce the central sensitization [18]. Moreover, the preoperative administration of N-methyl-D-aspartate antagonist evidently straightened the actions of local agent in reducing central sensitization in our clinical setting.

To support the preventive action of an analgesic treatment, the study end-point should exceed the duration of action of the target

Table 2: Cumulative morphine consumption in the early postoperative days

	Postoperative day				
	1	2	3	4	5
Group A	33.1 ± 6.3^a	29.8 ± 9.0^a	17.8 ± 7.5^a	12.9 ± 5.2^a	10.1 ± 5.6^a
Group B	35.3 ± 9.3	33.7 ± 11.0^b	18.2 ± 7.4^a	13.9 ± 5.5^a	11.2 ± 6.1^a
Group C	37.1 ± 8.5^b	33.3 ± 10.8^b	19.6 ± 9.3	12.2 ± 5.4^a	10.0 ± 4.3^a
Group D	36.5 ± 8.1^b	33.7 ± 7.1^b	22.3 ± 11.9^b	17.9 ± 11.1^b	14.2 ± 9.4^b

Data are expressed in milligrams.
Data are expressed as mean ± standard deviation.
^{a}MCB test significantly lower than the maximum.
^{b}MCB test significantly higher than the minimum.

Table 3: Visual analogue pain scale in the early postoperative time

VAS	Group	Postoperative time								
		2 h	6 h	12 h	24 h	2 days	3 days	4 days	5 days	30 days
Rest	A	3.9 ± 3.3^a	4.3 ± 2.7^a	4.2 ± 2.7	4.0 ± 2.6	3.1 ± 2.3	2.2 ± 1.8^a	1.4 ± 1.5	1.5 ± 1.7	1.1 ± 1.8
	B	5.2 ± 3.8^b	5.3 ± 3.0^b	3.8 ± 2.7	4.4 ± 2.5	3.4 ± 2.0	2.7 ± 1.9	1.8 ± 1.6	1.5 ± 1.4	1.1 ± 1.6
	C	4.0 ± 3.1^a	4.8 ± 2.1	4.4 ± 2.0	4.0 ± 2.1	3.0 ± 1.6	2.9 ± 1.8^b	1.5 ± 1.6	1.5 ± 1.6	1.5 ± 2.1
	D	3.5 ± 3.6^a	4.4 ± 3.0	3.5 ± 2.6	4.0 ± 2.4	3.5 ± 2.2	2.8 ± 2.1^b	1.9 ± 1.9	1.9 ± 1.9	1.5 ± 2.0
Movement	A	4.6 ± 3.5^a	5.3 ± 2.9	5.9 ± 2.4	5.5 ± 2.6	4.3 ± 2.4	2.9 ± 1.9^a	2.1 ± 1.8	2.2 ± 2.0	1.3 ± 2.0
	B	5.8 ± 3.7^b	6.1 ± 2.8	5.8 ± 2.2	5.7 ± 2.3	4.5 ± 2.0^b	3.3 ± 2.0	2.2 ± 1.6	2.2 ± 1.6	1.3 ± 1.6
	C	4.8 ± 3.2	5.6 ± 2.1	5.8 ± 1.7	5.2 ± 2.3	3.7 ± 1.8^a	3.3 ± 2.0	2.3 ± 1.8	2.6 ± 1.9	1.6 ± 2.3
	D	4.6 ± 3.8^a	5.6 ± 2.9	5.4 ± 2.4	5.5 ± 2.4	4.7 ± 2.3^b	3.5 ± 2.2^b	2.6 ± 2.1	2.6 ± 2.2	1.9 ± 2.1
Cough	A	4.8 ± 3.5	5.8 ± 2.8	6.5 ± 2.3	5.9 ± 2.3	4.8 ± 2.3	3.5 ± 2.2	2.6 ± 2.0	2.2 ± 2.0	1.5 ± 2.1
	B	5.8 ± 3.7	6.3 ± 2.8	5.9 ± 2.4	6.1 ± 2.3	5.0 ± 2.2	3.9 ± 2.2	3.0 ± 2.2	2.7 ± 2.2	1.6 ± 1.8
	C	5.0 ± 3.4	6.4 ± 2.1	6.6 ± 1.7	6.0 ± 2.1	4.6 ± 1.9^a	3.9 ± 2.1	2.8 ± 2.1	2.4 ± 2.2	1.5 ± 2.2
	D	4.7 ± 3.8	6.1 ± 2.8	6.1 ± 2.1	6.1 ± 2.2	5.4 ± 2.4^b	4.0 ± 2.4	3.3 ± 2.3	2.8 ± 2.3	2.1 ± 2.2

Data are expressed as mean ± standard deviation.
^{a}MCB test significantly lower than the maximum.
^{b}MCB test significantly higher than the minimum.

drugs; for this purpose, we chose a point in time greater than five half-lives of the drugs under examination according to the McCartney *et al.*'s review [19]. The stated half-life of levobupiva-caine is 2.6 and 2–4 h for dextromethorphan; consequently, we selected the second postoperative day as the critical point. Indeed, observing the CMC reported in Table 2, it is possible to note that the second postoperative day was exactly the point where Group A (preoperative dextromethorphan plus preopera-tive levobupivacaine) recorded the significantly lower amount of analgesic consumption versus the other groups. It is well known that N-methyl-D-aspartate antagonists may decrease opioid con-sumption by reduction in central hypersensitivity and opioid tol-erance; the results of McCartney *et al.*'s systematic review on the role of N-methyl-D-aspartate antagonists in preventive analgesia showed that ketamine as well as dextromethorphan produced a significant preventive analgesic advantage in 58 and 67% of ana-lysed trials, respectively [19]. The current study supports the find-ings of those positive trials and considering that we did not co-administer opioid with the N-methyl-D-aspartate antagonist at least for the first 6 h, it is possible to argue that the reduction in analgesic consumption was mostly due to dextromethorphan reduction in central sensitization rather than reduction in opioid tolerance.

The analysis of the visual analogue pain scale recorded during rest, rotation of the homolateral arm as well as during coughing, gave conflicting results. In a therapeutic scheme including patient-controlled drug administration, we consider this finding as not surprising; in such a setting, the amount of analgesic con-sumption (CMC) is the best parameter for pain quantification.

'Pain that recurs or persists along a thoracotomy scar at least 2 months following the surgical procedure' is the common defin-ition of the post-thoracotomy syndrome [16]. The prevalence of post-thoracotomy mild–moderate pain was 25.8% in our cohort, a finding lying in the mean of previous studies [8]. The 6- as well as 12-month checks revealed a decrease in post-thoracotomy syn-drome prevalence but we failed in the identification of any differ-ence among the groups. Even though a faint tendency was detected in Group A, we cannot state that the preventive analgesic schemes used in the current study affected the post-thoracotomy syndrome prevalence. Among a number of preoperative, intra-operative and postoperative factors analysed (including direct as well as indirect postoperative pain measurement), the female gender resulted the only item predicting post-thoracotomy syn-drome; this result is congruent with the findings of several studies showing that women have higher postoperative pain than men [20]. It is without doubt that rib retractors and pericostal sutures

are connected with nerve damage and pain in the postoperative period; indeed, trials involving nerve-sparing surgical techniques have demonstrated a reduction of post-thoracotomy syndrome [21]. Unfortunately, it is a common experience to observe a post-thoracotomy syndrome after a thoracoscopic lobectomy (mini thoracotomy without rib retractor), a video-assisted thoracic surgery or a simple chest tube positioning; such remarks support the hypothesis that, while nerve injury is a fundamental cause for the development of post-thoracotomy syndrome, other factors should contribute to its development. Further studies are needed to correctly understand and prevent the post-thoracotomy syndrome [22].

There are a number of studies addressing quality-of-life issues in the oncology setting while thoracic surgery trials specifically focussing on the quality of life are scarcely more than 20. The real value of the self-reported quality of life is still debated among clinicians and performance status (defined by the physician) and continues to be extensively used in trials as well as in clinical decision [23]. Recently, a couple of articles studied quality of life in open versus video-assisted pulmonary lobectomy, finding better results with the endoscopic technique; disconcerting was the result of the Barlesi trial that focused on the impact of information on quality of life and patients' satisfaction. This trial underlined the urgency of adjunctive research in this field [24, 25]. We observed a severe reduction in the health-related quality-of-life scores during the postoperative period; the scores reached the preoperative values 2 months after surgery and progressively increased to higher levels. Although this trend was expected, each group showed sporadic advantages over the other; considering that we found a bias in the recruitment, it became impossible to draw any conclusions on preventive analgesia and quality of life.

The present study has some limitations. We focused on an alternative local analgesic technique plus systemic analgesia although thoracic epidural analgesia is the gold standard for thoracotomy patients. Thoracic paravertebral block is also suggested and may be connected with fewer adverse effects than epidural analgesia. Actually, the IB is limited to the patients who require an alternative method because thoracic epidural analgesia or paravertebral block is not feasible for any reason. Besides the secondary endpoints, type-2 errors might exist: visual analogue pain score, functional data and post-thoracotomy syndrome showed no statistical difference that could be explained by a lack of power and the need of a larger population in each group. Finally, the choice of quality-of-life tests was questionable.

In conclusion, our results demonstrate that preoperative use of dextromethorphan associated with intercostal nerve block with levobupivacaine for thoracotomy patients provides preventive analgesic effects, decreasing postoperative analgesic consumption. This preventive scheme has been adopted in our department for patients who refuse epidural analgesia or when such technique is contraindicated.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr L. Molins (Barcelona, Spain): When experienced after thoracotomy, pain is considered to be one of the most intense acute postoperative pains possible. There are many strategies to control it; however, there is no universally accepted strategy, thus accounting for varying management policies among different groups.

Epidural analgesia is considered as the gold standard for thoracic analgesia. However, it has been largely demonstrated that a thoracic paravertebral infusion of a local anaesthetic provides similar pain relief with few side effects. Recently, there has been a better understanding of the pathophysiological mechanisms of postoperative pain, and a major emphasis has been given to a multi-modality approach to pain control. Several groups, including ours, have demonstrated that combining a local block, epidural or paravertebral anaesthesia, with a nonsteroidal, anti-inflammatory drug, is a safe and effective practice that reduces the cumulative morphine consumption. Different combinations have been tried in clinical studies. However, these postoperative schemes have not been completely successful in controlling postoperative thoracotomy pain. Newer strategies are needed. It is possible that when the injury has been done, there are few things to do later.

Preventive or pre-emptive analgesia as a strategy to reduce the magnitude and duration of postoperative pain was introduced in 1993 by Woolf, who showed evidence for a central component of post-injury pain hypersensitivity in experimental studies. This concept is based on the intuitive idea that if pain is treated before the injury occurs, the nociceptive system will receive less pain than if analgesia is administered post-injury. Preventive analgesia would apply well to the situation of elective surgery, since in this situation it is possible to control the series of events, and thus it is possible to deliver effective analgesia prior to injury. Owing to this "protective" effect on the nociceptive system, preventive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Therefore, immediate postoperative pain may be theoretically reduced and the development of chronic pain may be prevented.

Although some clinical studies have demonstrated significant effects on acute postoperative pain, no major clinical benefits of pre-emptive analgesia have been documented in prospective randomized studies. This excellent four-armed, double blinded, randomized, placebo-controlled trial was designed to prove this. The authors check the analgesic efficacy of the preoperative administration of dextromethorphan associated with intercostal nerve block with levobupivacaine in thoracotomy patients, comparing it with placebo and single preventive treatments. The study involves an important number of patients randomized in four arms, and there is an intensive follow-up period and ambulatory visits at 1, 2, 3 and up to 12 months.

The conclusion of the study is that the combined scheme provides preventive analgesic effects, decreasing the analgesic consumption during the early postoperative period after thoracotomy. In my opinion, the authors have been meticulous and have performed an elegant and intelligent study. Thanks to the large number of patients, the rigorous randomization, and the double-blinding, its conclusions are statistically strong and open the door for a new way to prevent the pain in thoracic surgery.

My questions. You state that the use of a visual analogue pain scale, VAS, gave conflicting results in your patients (that was in the manuscript) and that you mainly have confidence in the cumulative morphine consumption, the CMC. I also believe that CMC is the best and most objective parameter for pain quantification. However, VAS is commonly used in analgesia studies and tends to reflect the CMC. Your prospective study was meticulously planned. Is there any reason to explain this conflicting result with VAS?

And my second question. You demonstrate with this excellent prospective study that the preoperative use of dextromethorphan associated with an intercostal nerve block provides preventive analgesia effects in thoracotomy patients. However, you state in your conclusions that you have adopted this preventive scheme in your department only for patients who refuse epidural analgesia or when such a technique is contraindicated. My question is, why not use it routinely? Does dextromethorphan associated with intercostal nerve block severely interfere with epidural? In that case, why not use the promising preventive scheme associated with paravertebral block instead of epidural, as it has been proven as effective with a low risk of secondary effects?

Dr Nosotti: Regarding the VAS scale, I believe it is certainly a subjective evaluation system, so different patients can give different values to the same pain. Another problem specifically in our trial, is that the patients had patient-controlled analgesia, so they could directly modify the amount of analgesia following their subjective symptoms.

Also, the concept of preventive analgesia should be to avoid pain. Consequently, it is likely to lead to conflicting actions: to analyse the results of VAS and, at the same time, to prevent pain looking at this scale as an indicator. So I am not particularly confident in the VAS scale. Of course, we measure it every day in our department, but I believe it is not so useful in a scientific trial. Probably in this type of trial the cumulative morphine consumption could be the real factor we can correctly indagate.

Epidural analgesia is not widely used in our department as I mentioned before; our anaesthesiologists are not so interested in this type of analgesia. Of course, when they use it, the pain control is really excellent, but, as you know, a number of contraindications as well as a number of side effects may occur. Anyway, I believe that dextromethorphan can be used with epidural analgesia. This is my personal idea, not tested in this trial.

Paravertebral block is absolutely a good idea. I know you worked on this item for a long time, and I believe, in spite of epidural analgesia, that this should be the future for the patients, because paravertebral block has fewer side effects and it's very effective. This trial was started many years ago, and at that time we used intercostal block.

Dr T. D' Amico (Durham, NC, USA): It wasn't clear to me how you performed the preoperative intercostal blocks. When and how were they performed?

Dr Nosotti: Preoperative intercostal block 20 minutes before incision.

Dr D'Amico: So percutaneously?

Dr Nosotti: Percutaneously from T2 to T8.

Dr D'Amico: It has been shown in a prospective randomized trial that that's no better than placebo. Why did you use that technique?

Dr Nosotti: I would not agree with you. We are confident with the intercostal block. As you can see from the trial data, the intercostal block is effective. It is also possible to see an interesting effect: patients who had intercostal block after operation, had less pain immediately after surgery when matched with those who had intercostal block before operation. I was looking for preventive analgesia, therefore I wanted to make sure that the intercostal block would prevent the central sensitization.

Dr D'Amico: I understand the strategy, but that strategy of percutaneous block has been shown not to be effective.

Dr Nosotti: That is your opinion.

Dr S. Bölükbas (Wiesbaden, Germany): Many studies have shown that pleurectomy could be a source of severe postoperative pain. Therefore, many studies have excluded pleurectomy patients from further analysis. In your patient cohort, pleurectomy patients were not excluded. Were there any distribution differences between the different groups?

Dr Nosotti: No, there were no patients treated with pleurectomy, only lung resections: lobectomies, segmentectomies and pneumonectomies.

Dr E. Lim (London, UK): Just a comment in response to Dr D'Amico. In your group, you actually have two groups which answers the question: group B where you have levobupivacaine in the intercostal block and group D where you have saline in the intercostal block. And the results from group B, which is the one in which you have levobupivacaine, showed that the cumulative morphine consumption in fact is actually lower. So the results of your study suggest that the technique that you used for the intercostal block works.

Dr Nosotti: Yes.

Dr A. Turna (Istanbul, Turkey): Did you look at the lobectomy VATS patients and the thoracotomy patients separately in order to see which patients benefited most from the pre-emptive analgesia? Did you see a zeroing effect of this pre-emptive analgesia in VATS patients?

Dr Nosotti: This study finished before we started with VATS lobectomy. So I want now to implement a new study on this set of patients. Generally patients with a VATS lobectomy have less pain than thoracotomy patients, but sometimes they have pain. Consequently, to initiate a study on preventive analgesia in this set of patients would be useful. I will do that.

Dr G. Leschber (Berlin, Germany): What kind of incision do you normally use? Is it a posterior thoracotomy or an anterior?

Dr Nosotti: Posterior thoracotomy.

Dr Leschber: And you stated that there was an interval of 20 minutes prior to surgery.

Dr Nosotti: Yes.

Dr Leschber: Being in the operating room every day, it is difficult to say, okay, we will start in 20 minutes. Sometimes there are problems. How long does this analgesia last if there is some time lapse between your application of the block and then the start time of the surgery?

Dr Nosotti: The half-life of levobupivacaine is very long because the type of molecule permits very long anaesthesia, but the problem is not to start too late but to start too early, because we have to tie the hands of the surgeon waiting 20 minutes!