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ORIGINAL ARTICLE

Preventive skin analgesia with lidocaine patch for management of post-thoracotomy pain: Results of a randomized, double blind, placebo controlled study

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Keywords
Lidocaine patch; post-thoracotomy pain; pre-emptive analgesia; thoracic surgery.

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Abstract

Background: To evaluate whether pre-emptive skin analgesia using a lidocaine patch 5% would improve the effects of systemic morphine analgesia for controlling acute post-thoracotomy pain.

Methods: This was a double-blind, placebo controlled, prospective study. Patients were randomly assigned to receive lidocaine 5% patch (lidocaine group) or a placebo (placebo group) three days before thoracotomy. Postoperative analgesia was induced in all cases with intravenous morphine analgesia. The intergroup differences were assessed in order to evaluate whether the lidocaine patch 5% would have effects on pain intensity when at rest and after coughing (primary end-point) on morphine consumption, on the recovery of respiratory function, and on peripheral painful pathways measured with N2 and P2 laser-evoked potential (secondary end-points).

Results: A total of 90 patients were randomized, of whom 45 were allocated to the lidocaine group and 45 to the placebo group. Lidocaine compared with the placebo group showed a significant reduction in pain intensity both at rest ($P = 0.013$) and after coughing ($P = 0.015$), and in total morphine consumption ($P = 0.001$); and also showed a better recovery of flow expiratory volume in one second ($P = 0.025$) and of forced vital capacity ($P = 0.037$). The placebo group compared with the lidocaine group presented a reduction in amplitude of N2 ($P = 0.001$) and P2 ($P = 0.03$), and an increase in the latency of N2 ($P = 0.023$) and P2 ($P = 0.025$) laser-evoked potential.

Conclusions: The preventive skin analgesia with lidocaine patch 5% seems to be a valid adjunct to intravenous morphine analgesia for controlling post-thoracotomy pain. However, our initial results should be corroborated/confirmed by larger studies.

Introduction

Thoracotomy is one of the most painful surgical incisions. Postoperative pain reduces coughing and the mobilization of secretions, favoring respiratory complications, such as atelectasis and pneumonia. Thus, an effective analgesia is crucial to reduce postoperative morbidity and length of hospital stay (LOHS).

Thoracic epidural analgesia and thoracic paravertebral analgesia are the standard strategies for controlling post-thoracotomy pain, but the difficulty of performing them in all patients and potential complications limit their use. Systemic administration of opioids is the simplest and most common method to provide analgesia, but it may be associated with several undesirable effects, such as respiratory

depression, sedation, nausea, constipation, and vomiting.[1] In recent years, preventive analgesia has been proposed as an alternative strategy for postoperative pain control. It is based on the concept of administering analgesic drugs before the occurrence of nociceptive input in order to prevent central sensitization.[2] However, the effectiveness of pre-emptive analgesia for controlling pain after thoracic surgery remains unclear.[3] Post-thoracotomy pain has a multifactorial genesis including surgical incision, intercostal nerve injury, pleural inflammation, and injury to pulmonary parenchyma and the diaphragm. Thus, a multimodal analgesia that intercepts the pain stimuli generated by different locations could be more effective than a single strategy targeting only one site along the pain pathway.

In the present study, we evaluated a new multimodal analgesia for controlling post-thoracotomy pain as preemptive analgesia of the skin using a lidocaine patch 5% associated with systemic administration of morphine.

Methods

Study design

This was a double-blinded, placebo controlled, parallel-group, prospective study conducted at the Thoracic Surgery Unit and Anesthesia and Intensive Care Unit of Second University of Naples, Naples, Italy, from January 2013 to May 2015. All consecutive patients undergoing anatomical resection by standard muscle-sparing thoracotomy for treatment of non-small cell lung cancer were randomly assigned to the lidocaine or placebo group in a 1:1 ratio. No changes to methods after trial commencement, such as type of randomization or eligibility criteria, were made.

The study design, planned according to the CONSORT-SPIRIT guideline,[4] was approved by the local ethics committee of our institution (approval code number: 436/2012) and was registered at ClinicalTrial.gov (NCT02751619). The pros and cons of the lidocaine patch were explained to patients by the coordinator of the study and/or the staff participating in the study. Participants were informed that their participation was voluntary and that they might withdraw consent to participate at any time during the study without any consequences for their care. All patients gave written informed consent before entering into the study.

Participants

All consecutive patients aged >18 years and undergoing anatomical resection by standard muscle-sparing thoracotomy for non-small cell lung cancer were eligible. Exclusion criteria included: (i) allergy to lidocaine; (ii) American Society of Anesthesiologists >3; (iii) history of previous thoracic surgical procedures and/or of chronic pain or taking regular analgesics; (iv) pneumonectomy or concomitant decortication and/or chest wall injury or resection; (v) psychiatric illness; and (vi) participation to other studies. Demographic, functional, clinical and pathological data, LOHS, postoperative morbidity, and mortality were recorded for each patient.

Intervention

Patch placement

For patients assigned to the active group, a lidocaine patch 5% (Lidoderm; Endo Pharmaceuticals Inc., Malvern, PA, USA) measuring 10 × 14 cm and containing 700 mg of lidocaine was applied to cover the planned skin incision, marked with a pen by the surgeon. The patch was applied for 12 hours during the night, and removed for a subsequent 12 hours during the day. This process was repeated for three days before surgery. In the control group, a placebo patch, that was identical in appearance to the active patch, but did not contain lidocaine, was applied for the same amount of time. The pain service, surgical team, and patients were all blinded to the treatment group assigned.

General anesthesia

All patients underwent the same anesthetic protocol. All operations were performed in the early morning after removal of the patch. The general anesthesia was inducted with i.v. midazolam 0.05 mg/kg, i.v. fentanyl 1–1.4 μg/kg, i.v. propofol 2.5 mg/kg, and i.v. rocuronium bromide 0.6 mg/kg. The patient was maintained with desflurane 4–6%, sufentanil 0.5–1 μg/kg, and rocuronium bromide 0.6–0.8 mg/kg, based on heart rate and blood pressure stability. A selective ventilation was performed with a double-lumen endobronchial tube in all cases, and no additional analgesics were administered during surgery.

Surgical technique

All patients had the same length of skin incision and a standard muscle-sparing lateral thoracotomy. The latissimus dorsi muscle and the underlying serratus anterior muscle were spared, and the chest was entered over the top of the unresected and unfractured sixth rib. A standard Finocchietto chest retractor was then placed and slowly opened to avoid rib fracture. After completion of the appropriate anatomical lung resection, a single 28-Fr chest tube was left in the pleural cavity. The same chest closure was performed for all patients in a standard manner using intra-costal sutures.

Postoperative pain control

Patients were extubated in the operating room and transferred to the surgical ward. The postoperative analgesia

was performed with intravenous morphine administered through Patient Controlled-Analgesia (Automed 3300; AceMedical Co. Seoul, Korea) delivery. Morphine 1 mg was given for each request, and continuous infusion was at a rate of 1 mg/h. Both groups had a 10-minute lockout period and a safe higher limit of 20 mg in 4 hours. If VAS scores exceeded 4/10 scores, rescue analgesia was intravenously administered according to a standardized institutional protocol for pain treatment until the pain was relieved to a level falling below a VAS score <4. Patient-controlled analgesia (PCA) was continued for up to two days, until patients could tolerate oral opioid medications and/or anti-inflammatory analgesics. However, these medications were not considered in the analysis.

Primary end-point

The primary end-point was to evaluate whether lidocaine compared with a placebo was able to reduce the pain during the first 72 postoperative hours. The pain levels were measured using a 10-score visual analog scale (VAS) ranging from 0 = absence of pain to 10 = maximal level of pain. The measurements were carried out at rest, and after coughing at 6, 12, 24, 36, 48, and 72 post-operative hours.

Secondary end-points

The secondary end-points were to evaluate: (i) the frequency of PCA activation; (ii) total morphine consumption; (iii) recovery of post-operatory respiratory function; (iv) any changes in sensory pathways; (v) LOHS; and (vi) postoperative morbidity.

Frequency of PCA and morphine consumption

The frequency of pushing the button of the PCA system (number/hour) and the total morphine consumption (the sum of additional i.v. morphine bolus infusions and the morphine delivered by the PCA system) were evaluated in the following postoperative intervals: 0–6 hours, 6–12 hours, 12–24 hours, 24–36 hours, and 36–48 hours.

Respiratory function

Bedside pulmonary functional test of flow expiratory volume in one second and forced vital capacity expressed as a percentage of the predicted value were measured using Spirolab III, Spirometer (Cosmed; Albano Laziale, Rome, Italy) before operation, at 72, 96, and 120 post-operative hours, and at discharge. The best of three efforts was used for the analysis.

Laser-evoked potential tests

Laser stimulation, delivered by neodymium-doped yttrium aluminium garnet (Nd:YAG) laser, was applied at the level of the thoracotomy scar, the main territory corresponding to the distribution of pain. Three seconds after each stimulus, a weak tone prompted the patient to rate the pain sensation on a 10-score VAS scale with 4 denoting the pain threshold. Pain threshold intensity was determined by three series of stimuli ascending in steps of 30 mJ from below the sensation threshold to 90 mJ above the pain threshold and back again to below the sensation threshold. Thus, the pain threshold was the average of the six values at which the laser pulse was either first noted as a pinprick-like pain sensation (VAS >4) during an ascending series or as no longer painful (VAS <4) during a descending series. For laser-evoked potential (LEP) analysis, stimuli were given in blocks of 40 with randomized intensities (450 mJ and 600 mJ). The stimulus was supplied at irregular randomized intervals (between 10 and 20 s) to avoid the neurophysiological phenomenon called habituation that could compromise the signals recording. Electroencephalographic registration was made from four midline electrodes (FCs; Cz; CPz; and Pz) according to the international 10–20 system, using a standard electroencephalographic cap and Neuroscan software. We considered only the data from the vertex position (Cz), where pain-related LEP are known to be maximal. Electro-oculogram was recorded from supra- and infraorbital electrodes for offline artifact rejection. Room temperature was 22–23°C, and skin temperature was always >30°C. The patients were instructed to keep their eyes open, to focus on a fixed point on the wall, and to avoid blinking. The resulting LEPs were evaluated for amplitude and latency differences between the vertex negativity (N2) appearing around 240 ms, and the following positivity (P2) appearing around 360 ms after stimulus onset. The LEPs were performed at 1, 3, and 6 months after operation, and in the same setting the level of pain was also measured with VAS.

Sample size

We calculated our sample size based on the primary outcome measure as the VAS score. The power of the study was calculated using PASS 11 (NCSS, LLC. Kaysville, Utah, USA). For the parallel design, a sample size of 40 (40 per group) was calculated, assuming an intention to detect an effect size of 0.65 in the mean difference of the VAS score with 80% power, and a type I error rate of 0.05. In anticipation of missing data on the primary end-point during the study period, we extended the number of patients to 90 before any comparative analysis.

Randomization

Participants were randomly assigned with a 1:1 allocation to the lidocaine or placebo group by our research

pharmacy, and it was based on computer-generated codes. Each patient had an equal probability of being assigned to either the active treatment group or the placebo group. The details of the series were unknown to the investigators. The group assignments were kept in sealed envelopes, each bearing only the case number of the outside. After recruitment, the patients were given a case number, and 1 hour before placing the patch, the numbered envelope was opened and the card inside determined the group into which the patient would be placed. The lidocaine and placebo patch, labeled with the case number, were similar to keep all investigators blind to the patient's assigned group.

Statistical analysis

Data were summarized as the mean and standard deviation for normally distributed continuous variables; and absolute number and percentage for categorical variables, as appropriate. Statistical differences were evaluated using the χ^2-test for categorical variables, and *t*-test for non-categorical variables. Repeated measures analysis of variance (ANOVA test) corrected with the Bonferroni post-hoc test was used for comparison of variables measured at different time-points of follow up.

All patients randomized were included in the analysis according to intention-to-treat analysis. For the primary end-point (VAS score evaluation), we performed a conservative intention-to-treat analysis using all randomized patients. In that analysis, for the primary end-points we assigned the worst possible observed score to missing data points for those assigned to the lidocaine group, and the best possible observed score to missing data for placebo patients. For the secondary outcomes, missing data were completed using the last observation carried forward analysis. The difference was considered significant for *P*-values ≤0.05. MedCalc statistical software (version 12.3; Broekstraat 52, Mariakerke, Belgium) was used for the analysis.

Results

A total of 94 patients were eligible for the present study. Four patients were excluded because of allergy to lidocaine (n = 1), previous thoracic surgical procedure (n = 1), rib fracture during thoracotomy (n = 1), and refusing to perform the LEP test (n = 1). Thus, 90 out of 94 (96%) patients were randomly allocated into the lidocaine (n = 45) and placebo group (n = 45). One patient for each study group did not complete the follow-up LEP tests, but they were included in the analysis according to study design. A flow chart of the study according to the CONSORT guidelines[4] is reported in Figure 1. The demographic, clinical, and pathological data of the two study groups are summarized in Table 1.

Primary end-point

The results of the VAS scores are reported in Table 2 and Figure 2. The ANOVA test showed that lidocaine compared with placebo had significantly lower VAS scores at rest (P = 0.013; Fig 2a). However, considering *P*-values adjusted for comparison at multiple times by the Bonferroni post-hoc test, we found no significant difference between the two study groups at 6 post-operative hours (P = 0.1) and at 72 post-operative hours (P = 0.2).

Similar results were found for VAS scores after coughing (Fig 2b). They were found to be significantly lower in the lidocaine group than in the placebo group (P = 0.015; ANOVA test), but a post-hoc test showed no significant difference between the two study groups at 6 (P = 0.1) and at 72 post-operative hours (P = 0.3).

Secondary end-points

The frequency of PCA and morphine consumption

The results are shown in Table 2 and in Figure 3. The administration frequency of PCA (P = 0.001; Fig 3a) and the total administration of morphine (P = 0.001, Fig 3b) was higher in the placebo group compared with the lidocaine group for all follow-up time points.

Respiratory function

The results are summarized in Table 2 and in Figure 4. The recovery of flow expiratory volume in one second (P = 0.025; Fig 4a) and the forced vital capacity (P = 0.037, Fig 4b) was faster in the lidocaine group than in the placebo group.

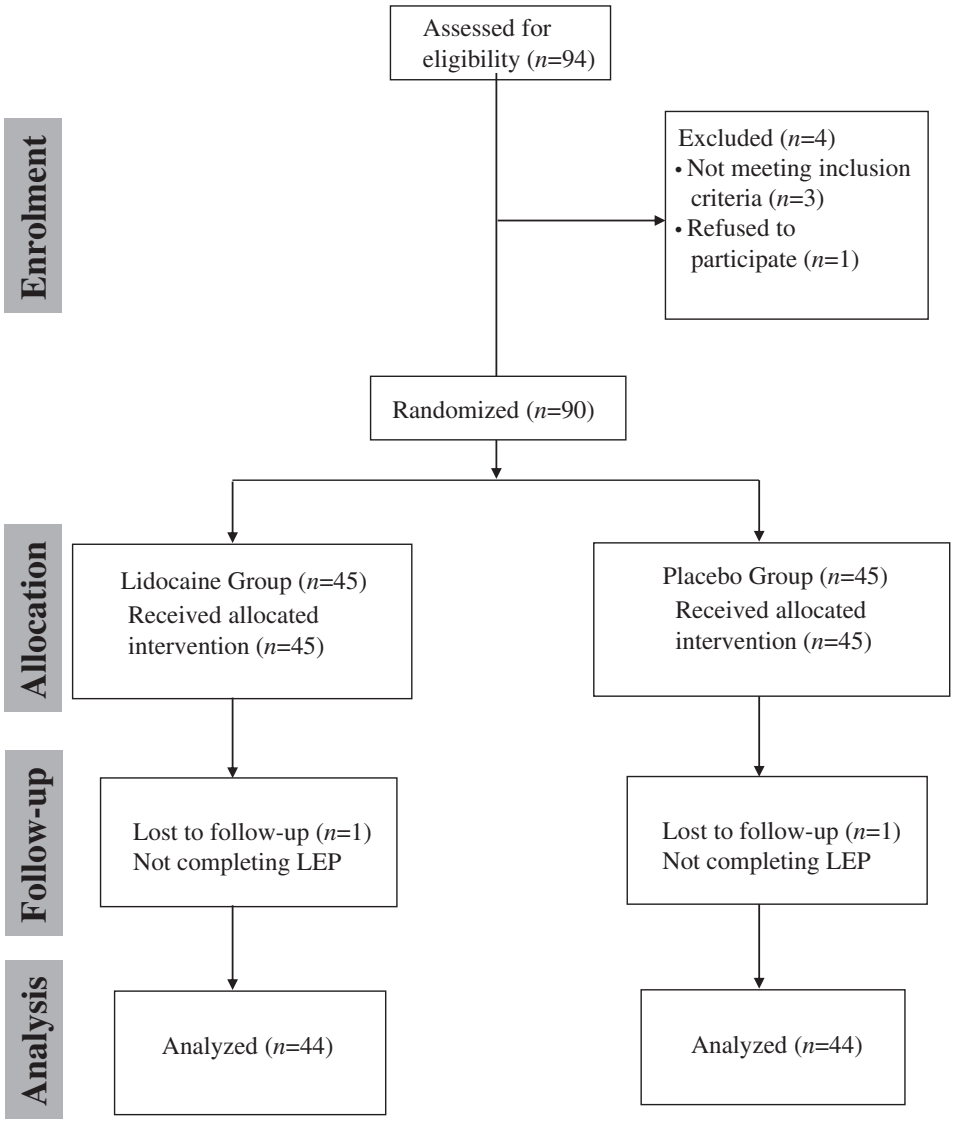
LEP tests

As reported in Table 3, in the lidocaine group, no significant difference was found between baseline and post-operative values of N2 and P2 LEP. In contrast, in the placebo group, a significant reduction of N2 and P2 in amplitude, and a significant increase of N2 and P2 in latency were observed. The comparison between the two study groups (Table 2) showed that the placebo group compared with the lidocaine group had a significant reduction of N2 (P = 0.001; Fig 5a) and of P2 (P = 0.035, Fig 5b) in amplitude, and a significant increase of N2 (P = 0.023; Fig 5c) and of P2 (P = 0.025; Fig 5d) in latency.

Other data

No significant difference was found regarding operative time (P = 0.87), length of chest drainage (P = 0.93) and LOHS (P = 0.93), and postoperative complications (P = 0.33). In addition, the use of the lidocaine patch was not associated with specific side-effects (Table 1).

Figure 1 Flow chart of the study.



Discussion

In the past decade, a growing number of diagnostic and curative procedures have been performed using video-assisted thoracoscopic surgery,[5,6] but thoracotomy still remains the most common incision among thoracic surgeons, and the preferred approach in many centers for resecting advanced stage non-small cell lung cancer or for performing complex procedures, such as broncho-vascular resection.[7]

Pre-emptive analgesia is based on the intuitive idea that if pain is treated before the injury occurs, the nociceptive system will perceive less pain than if analgesia is given after the injury has already occurred.[8,9] The injection of lidocaine before surgical incision showed significant pain reduction after video-assisted thoracoscopic surgery sympathectomy,[10,11] but Cerfolio *et al.* did not find any benefits in patients undergoing thoracotomy.[12] In theory, the pre-emptive effect of lidocaine controlled the pain stimuli generated from the surgical incision, but not those caused by intercostal nerve injury or visceral components, such as the lung, pleura, and diaphragm, during the surgical maneuvers. To overcome this limit, in the present study, we planned a new strategy, not reported before, as the association between the pre-emptive skin analgesia with a lidocaine patch and the PCA morphine analgesia. The clinical hypothesis was that this multimodal analgesia, acting at different sites of pain pathways, such as thoracotomy (through the lidocaine patch) and the cortex (through the morphine), could better control thoracotomy pain compared with the administration of morphine alone.

Table 1 Characteristics of the study population

Variables	Total	Lidocaine group	Placebo group	*P*-value
No. patients	90	45	45	—
Male	70 (77%)	31 (69%)	39 (87%)	0.04
Age (years)	62.3 ± 7.9	63 ± 4.9	60.2 ± 11.3	0.69
Charlson Comorbidity Index	1.3 ± 4.2	1.3 ± 1.8	1.3 ± 2.7	0.89
ASA classification				0.33
• ASA 1	79 (88%)	41 (91%)	38 (84%)	
• ASA 2	10 (11%)	4 (9%)	6 (14%)	
• ASA 3	1 (1%)	0	1 (2%)	
Clinical stage				
• Ia	15 (16.5%)	6 (13%)	9 (20%)	0.39
• Ib	25 (28%)	16 (36%)	9 (20%)	0.10
• IIa	35 (39%)	16 (36%)	19 (42%)	0.51
• IIb	15(16.5%)	7 (15%)	8 (18%)	0.77
FEV1%	91 ± 16.3	91 ± 2.9	91 ± 11	0.79
FVC%	90 ± 8.5	90 ± 3.7	90 ± 6.9	0.91
Type of resection				
• Lobectomy	89 (99%)	44 (98%)	45 (100%)	0.31
• Bilobectomy	1 (1%)	1 (2%)	0	
Histology				
• Adenocarcinoma	50 (55%)	29 (64%)	21 (47%)	0.09
• Squamous cell carcinoma	35 (39%)	12 (27%)	23 (51%)	0.01
• Large cell carcinoma	5 (6%)	4 (9%)	1 (2%)	
Pathological stage				
• Ia	14 (16%)	6 (13%)	8 (18%)	0.56
• Ib	22 (24%)	15 (33%)	7 (16%)	0.05
• IIa	33 (37%)	15 (33%)	18 (40%)	0.51
• IIb	19 (21%)	8 (19%)	11 (24%)	0.44
• IIIA	2 (2%)	1 (2%)	1 (2%)	1.0
Operative time	186 ± 24.5	188 ± 31	184 ± 19.4	0.87
Chest drain length (days)	5.8 ± 2.6	5.7 ± 2.8	5.9 ± 3.1	0.91
Hospital stay (days)	7 ± 4.6	6.9 ± 2.1	7.1 ± 1.9	0.93
Postoperative complications				
• Atelectasis	7 (8%)	2 (4%)	5 (11%)	0.24
• Air leaks	3 (3%)	2 (4%)	1 (2%)	0.55
• Atrial fibrillation	1 (1%)	—	1 (2%)	0.31

Data are expressed as mean ± standard deviations and/or as percentages. *P*-value was calculated using the χ^2-test and *t*-test. ASA, American Society of Anesthesiologists; FEV1%, forced expiratory volume in one second; FVC, forced vital capacity.

Our results showed a better control of postoperative pain, a significant reduction of the frequency of PCA activation and of morphine consumption, and a faster recovery of respiratory function in the active group compared with the placebo group. The analgesic effect of the lidocaine patch was mainly due to the pre-emptive block of noxious input from the skin incision.[13–16] In fact, lidocaine was absorbed by painful fibers of the skin, and, through the block of the sodium channels of the neuronal membrane, prevented the generation and conduction of action potential from the periphery (site of incision) to the cortex.[13–16] The block of the afferent pain transmission resulted in a reduction of pain perception. An additional mechanism was the reduction of the acute phase of inflammatory reactions, as lidocaine inhibited the activation of neutrophil and reduced the local release of cytokines.[17–19] Furthermore, we found a significant reduction of VAS score not only at rest, but also after coughing, showing the effectiveness of the lidocaine patch to control pain also at a deeper level than surgical incision. Our results were confirmed by previous studies that found that the lidocaine patch provided good analgesic relief and an improvement of pulmonary functional tests in

Table 2 Comparison of two study groups

Variables	Time	Lidocaine group	Placebo group	*P**	*P***
VAS at rest	6 POHs	3.8 ± 0.7	4.3 ± 0.6	0.18	0.013
	12 POHs	3.7 ± 0.4	4.4 ± 0.5	0.01	
	24 POHs	3.0 ± 0.4	3.8 ± 0.3	0.003	
	48 POHs	2.4 ± 0.6	3.0 ± 0.4	0.01	
	72 POHs	1.6 ± 0.6	2.0 ± 0.5	0.25	
VAS after coughing	6 POHs	4.8 ± 0.7	5.3 ± 0.6	0.15	0.015
	12 POHs	4.7 ± 0.4	5.4 ± 0.5	0.01	
	24 POHs	4.0 ± 0.4	4.8 ± 0.2	0.003	
	48 POHs	3.4 ± 0.6	4.0 ± 0.4	0.01	
	72 POHs	2.6 ± 0.6	3.0 ± 0.5	0.37	
Frequency of PCA	6 POHs	4.3 ± 0.9	5.2 ± 0.7	0.03	0.001
	6–12 POHs	3.3 ± 0.6	6.4 ± 0.5	0.004	
	12–24 POHs	2.2 ± 0.9	4.3 ± 0.8	0.001	
	24–36 POHs	1.5 ± 0.5	3.2 ± 0.7	0.005	
	36–48 POHs	0.5 ± 0.2	0.7 ± 0.3	0.04	
Morphine consumption	6 POHs	20.3 ± 2	24.4. ± 4.1	0.02	0.001
	6–12 POHs	19 ± 2.1	22.4 ± 3.2	0.003	
	12–24 POHs	18 ± 2.4	21.7 ± 2.1	0.002	
	24–36 POHs	12 ± 1.5	16 ± 1.7	0.001	
	36–48 POHs	2.1 ± 0.9	3.5 ± 0.8	0.03	
FEV1%	Baseline	89.9 ± 9.7	96.4 ± 6.4	0.85	0.025
	72 POHs	77.7 ± 8.8	70.1 ± 4.7	0.023	
	96 POHs	79.5 ± 7.8	70.4 ± 4.8	0.021	
	120 POHs	79.8 ± 7.4	71.7 ± 4.2	0.025	
	Discharge	81.5 ± 7.8	72.4 ± 4.8	0.024	
FVC%	Baseline	94.9 ± 6.6	97.4 ± 6.4	0.92	0.037
	72 POHs	82.8 ± 7.4	74.7 ± 4.2	0.029	
	96 POHs	82.7 ± 6.9	76.2 ± 6.2	0.035	
	120 POHs	85 ± 4.9	81.8 ± 8.5	0.038	
	Discharge	87 ± 4.9	83.8 ± 8.2	0.040	
P2 amplitude	Baseline	9.6 ± 0.7	11 ± 1.7	0.27	0.001
	1 POM	8.4 ± 0.9	3.9 ± 0.6	0.0003	
	3 POMs	8.7 ± 0.8	4.8 ± 0.9	0.0004	
	6 POMs	9.7 ± 0.7	5.6 ± 0.3	0.001	
P2 latency	Baseline	455 ± 8.3	441 ± 7.9	0.071	0.025
	1 POM	465 ± 8.3	495 ± 5.5	0.015	
	3 POMs	463 ± 8.6	485 ± 4.3	0.016	
	6 POMs	454 ± 8.7	482 ± 5.3	0.023	
N2 amplitude	Baseline	−28 ± 1.3	−27 ± 1.9	0.67	0.035
	1 POM	−31 ± 1.9	−50 ± 3.9	0.024	
	3 POMs	−30 ± 1.6	−49 ± 1.7	0.025	
	6 POMs	−28 ± 5.9	−41 ± 2.9	0.027	
N2 latency	Baseline	262 ± 8.7	257 ± 5.4	0.73	0.023
	1 POM	271 ± 7.3	296 ± 8.9	0.023	
	3 POMs	265 ± 5.8	293 ± 3.8	0.027	
	6 POMs	263 ± 8.9	289 ± 4.3	0.025	

*Bonferroni post-hoc test **ANOVA test. POH, postoperative hour; POM, postoperative month.

patients with rib fractures.[20,21] Lidocaine's half-life was 1.5–-2 hours, but we observed a significant reduction of pain for a longer time, supporting the preventive action of our analgesic treatment. As a matter of fact, preventive analgesia is shown when postoperative pain and/or analgesic use are reduced beyond the duration of action of the target drug; that is, approximately 5.5 half-lives of the target drug.[3] In the present study, post-hoc tests showed a significant reduction of VAS score up to 48 hours after the operation. Thus, the pre-emptive inhibition of the sensitization of central nociceptive pathways through the blockage of peripheral nociceptive pathways rather than the simple local effect of lidocaine explained the analgesic effects. Conversely, despite a positive trend, pre-emptive analgesia did not bring about any significant benefits within the first six postoperative hours ($P = 0.1$). In theory, the effects of general anesthesia

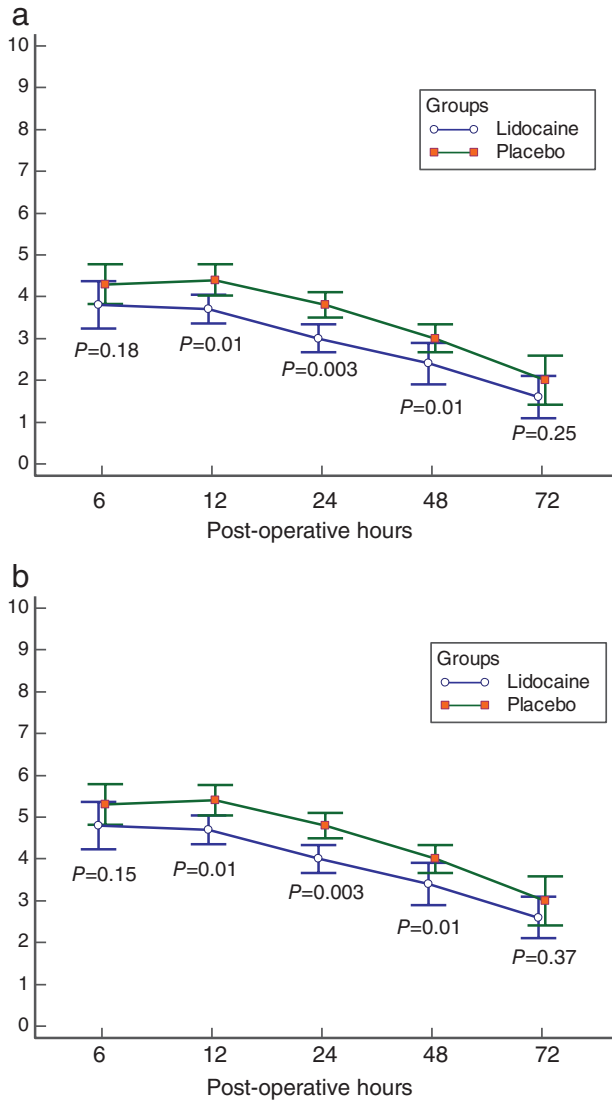


Figure 2 The lidocaine group compared with the placebo group had significantly lower visual analog scale (VAS) scores (**a**) at rest ($P = 0.013$) and (**b**) after coughing ($P = 0.015$). (—○—) Lidocaine and (—■—) placebo.

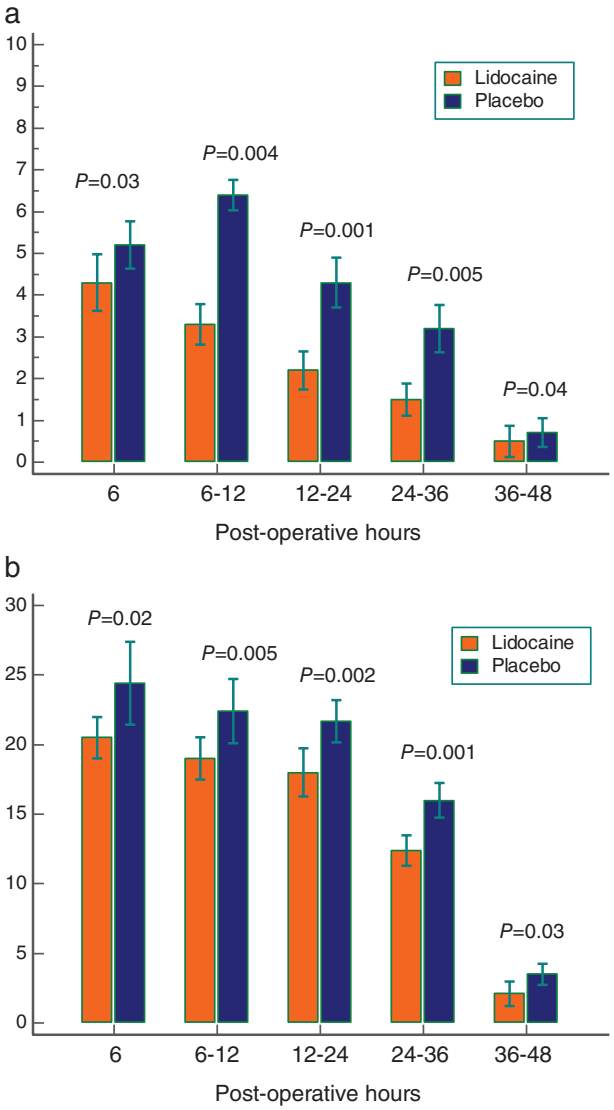


Figure 3 (**a**) The administration frequency of patient-controlled analgesia (PCA) expressed as number/hour ($P = 0.001$) and (**b**) the total consumption of morphine expressed as mg ($P = 0.001$) were higher in the placebo group compared with the lidocaine group. (■) Lidocaine and (■) placebo.

on pain were still present during the early postoperative hours and thus masked the analgesic effect of lidocaine.

In the placebo group, we found significant changes, such as a reduction in amplitude and increase in latency of N2-P2 components compared with the pre-operative values, whereas the lidocaine group showed similar postoperative N2-P2 values compared with baseline. However, the VAS values between the two groups were similar during the same follow-up times. It means that LEPs were not associated with subjective pain perception, but they reflected the state of the sensory pathway. Similar results were obtained in tooth pulp stimulation, where evoked potential became reduced in amplitude while pain ratings were unchanged.[22]

In theory, the lack of sensitization of nociceptive peripheral pathways due to the pre-emptive effect of lidocaine could explain the normal LEPs observed in the active group. In contrast, in the placebo group, the nerve sensitization could alter the integrity and the function of small painful fibers, such as A-delta and C fibers, with consequent LEPs changes. In peripheral neuropathies, where the small fiber disease shows a characteristic predominance of loss in autonomous peripheral nerve function, LEP may be absent or attenuated in amplitude, indicating impaired function of both A-delta and C-fibers. In patients with carpal tunnel syndrome, LEP amplitude was reduced due to the stimulation of the third

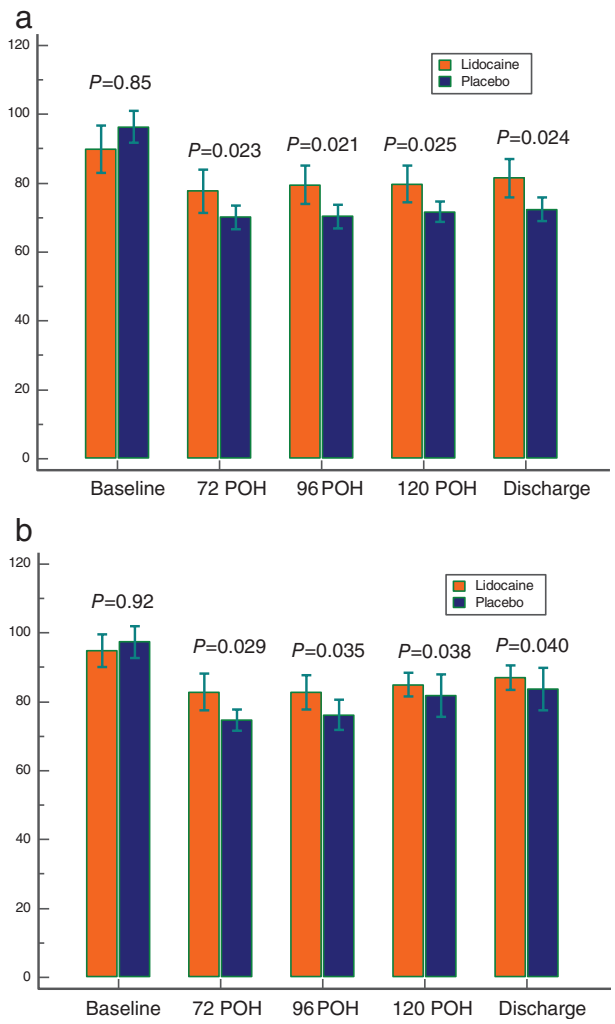


Figure 4 The recovery of (**a**) forced expiratory volume in one second (FEV1%; $P = 0.025$) and of (**b**) forced vital capacity (FVC%; $P = 0.037$) was faster in the lidocaine group than in the placebo group. (■) Lidocaine and (■) placebo. POH, postoperative hour; POM, postoperative month.

finger.[23] Agostino *et al.* investigated LEPs in 45 diabetes patients with various degrees of peripheral nerve damage, and reported that the most frequent abnormalities were absent or decreased amplitude LEPs, as expected in axonopathies.[24] However, the short follow-up period of our study was unable to show whether LEP alteration could predispose to post-thoracotomy syndrome in the placebo group.

The use of the lidocaine patch was safe and no collateral effect was observed in the active group. Each patch contains 700 mg lidocaine and a total of 3 ± 2% of the dose was absorbed. In accordance with previous studies, the patch was used with an interval of 12 hours per three consecutive days in order to avoid the habituation of the nerve to lidocaine effects, and to reduce the risk of toxic effects.[11–14] The blood levels of the lidocaine 5% patch were minimal when applied at a maximum dose of three patches each day for 12 hours, and also when four patches each day were applied for 18 hours. Pharmacological studies found that the systemic circulation reached only one out of 10 of the concentration required in the treatment of cardiac arrhythmias.[13–16]

Our results are in contrast with those of Cerfolio *et al.*, who did not find significant benefits associated with pre-emptive skin analgesia for controlling postoperative pain.[12] Several reasons may explain the different results. We believe that the main and most important difference was the procedure adopted for obtaining pre-emptive skin analgesia. In contrast to the traditional percutaneous injection of lidocaine, as that performed by Cerfolio *et al.*, the lidocaine patch was designed to deliver the same concentration of anesthetic, thus facilitating a uniform pre-analgesia effect within all parts of the surgical incision.[12] Again, Cerfolio *et al.* injected lidocaine 5 minutes before incision, whereas in the present study the skin was pre-emptively anesthetized three days before incision.[12] In theory, the longer exposure to lidocaine could perpetuate the complete block of peripheral pain pathways, and thus maximize the pre-emptive effect of lidocaine. In addition, the different thoracotomy performed (postero-latheral in Cerfolio's study[12] vs. lateral with muscle sparing in the present study), postoperative analgesia administered (epidural in Cerfolio's study[12] vs. systemic morphine analgesia in the

Table 3 P2 and N2 value of study groups

Groups	Variables	Baseline	Postoperative			*P*-value
			1-month	3-month	6-month	
Lidocaine	P2 amplitude	9.6 ± 0.7	8.4 ± 0.9	8.7 ± 0.8	9.7 ± 0.7	0.8
	P2 latency	455 ± 8.3	465 ± 8.3	463 ± 8.6	454 ± 8.7	0.2
	N2 amplitude	−28 ± 1.3	−31 ± 1.9	−30 ± 1.6	−28 ± 5.9	0.3
	N2 latency	262 ± 8.7	271 ± 7.3	265 ± 5.8	263 ± 8.9	0.8
Placebo	P2 amplitude	11 ± 1.7	3.9 ± 0.6	4.8 ± 0.9	5.6 ± 0.3	0.0001
	P2 latency	441 ± 7.9	495 ± 5.5	485 ± 4.3	482 ± 5.3	0.0001
	N2 amplitude	−27 ± 1.9	−50 ± 3.9	−49 ± 1.7	−41 ± 2.9	0.0004
	N2 latency	257 ± 5.4	296 ± 8.9	293 ± 3.8	289 ± 4.3	0.0002

The *P*-value was calculated with ANOVA test.

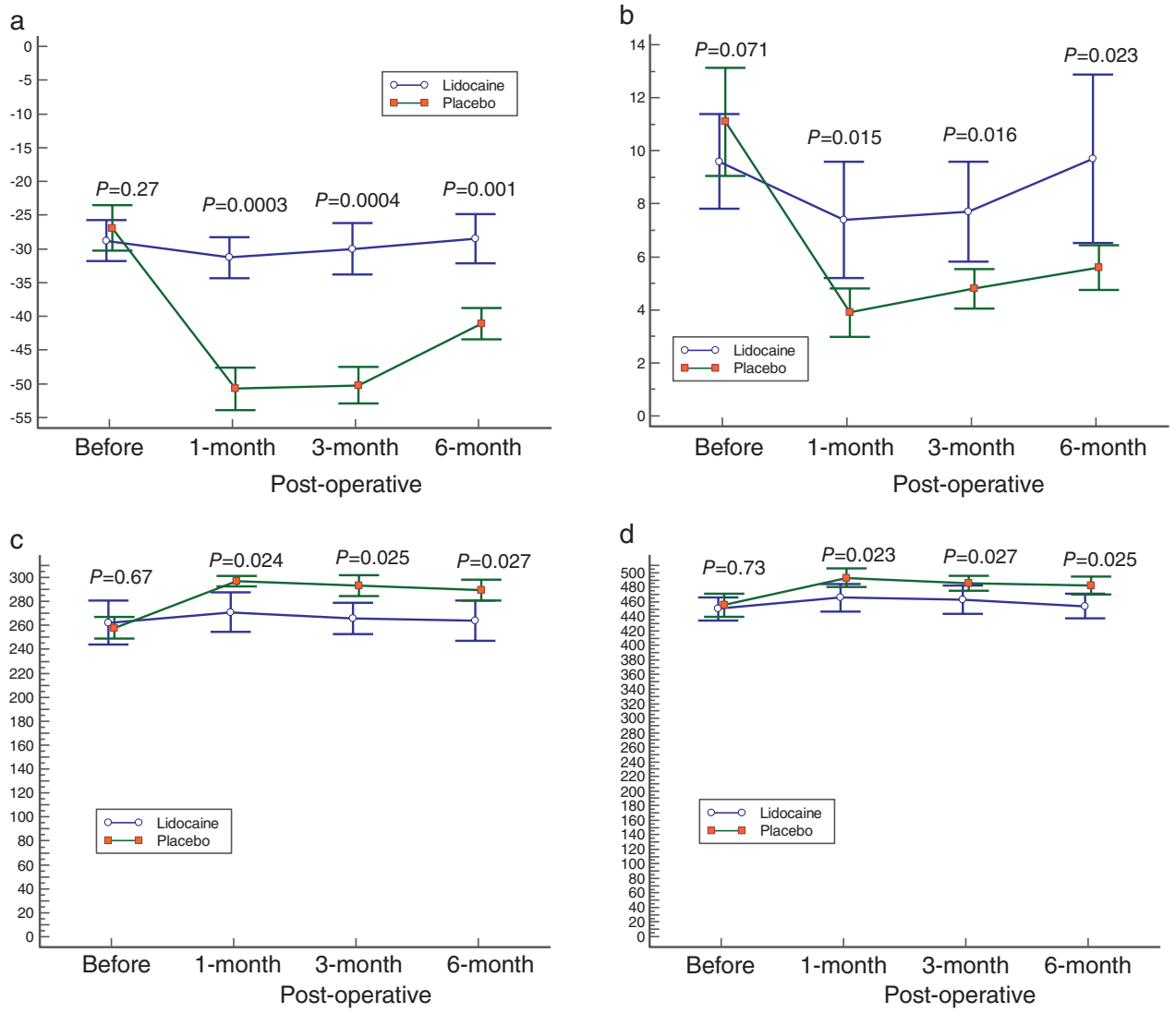


Figure 5 The placebo group compared with the lidocaine group had a significantly lower value in the amplitude of (**a**) N2 (P = 0.001) and of (**b**) P2 (P = 0.035), and a higher value in the latency of (**c**) N2 (P = 0.023) and of (**d**) P2 (P = 0.025). (—○—) Lidocaine and (—■—) placebo.

present study), and measure of pain (McGill model in Cerfolio's study[12] vs. VAS scale in the present study) could also explain the differences in the results.

Our data should be considered with caution due to the following limitations: (i) all patients received a postoperative regimen based on i.v. morphine that may be inadequate for controlling pain and thus it makes it easier to find differences between the two study groups; (ii) the pain was measured with VAS, which can be influenced by many variables in contrast to more sophisticated means of quantifying pain, such as the McGill pain questionnaire; (iii) only one patch for 12 hours was used in all patients without considering the variations in patients' skin thickness that could affect the diffusion of lidocaine through the tissues. Ideally, in patients with greater skin thickness, more than one patch could be used due to the low rate of lidocaine diffusion.

In conclusion, pre-emptive skin analgesia using a lidocaine patch is a safe, quick, and simple procedure for controlling post-thoracotomy pain. It improves pain relief while reducing morphine requirements and morphine-related adverse effects. Thus, it could be considered an adjuvant modality to systemic morphine analgesia, especially for patients where epidural and/or paravertebral block analgesia are contraindicated. Obviously, larger studies are required to confirm our results before this strategy can be widely recommended in thoracic surgery.

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Disclosure

No authors report any conflict of interest.

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