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ORIGINAL ARTICLE

Comparison of the analgesic effects of cryoanalgesia vs. parecoxib for lung cancer patients after lobectomy

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Abstract This study was designed to compare the analgesic effects of cryoanalgesia and parecoxib in lung cancer patients after lobectomy. A total of 178 lung cancer patients awaiting large-sized lobectomy were enrolled in the study. The patients were randomly divided into Group A (intercostal nerve cryoanalgesia) and Group B (parecoxib). The analgesic and adverse effects were compared between the two groups. The pain score of Group A was significantly lower than that of Group B ($P < 0.05$). The patients in Group A used significantly less morphine than those in Group B ($P < 0.05$). There were also significantly fewer complications in Group A than in Group B ($P < 0.05$). Cryoanalgesia of the intercostal nerves can be considered an economical, safe and simple technique for the long-term management of post-lobectomy pain.

Keywords Lobectomy · Analgesic effects · Cryoanalgesia · Parecoxib

Introduction

Long-term pain after thoracotomy is very common, but remains a critical challenge [1]. Effective pain management after thoracotomy can produce remarkable benefits, but is difficult to achieve [2, 3]. It has been reported that chronic post-thoracotomy pain can be neuropathic or nociceptive

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[4–6], which provides the basis for the application of cryoanalgesia.

Cryoanalgesia applies a cryoprobe which employs the Joule–Thomson effect, whereby carbon dioxide or nitrous oxide is released at a high pressure (ranging from 4000 to 6000 kPa) and allowed to expand quickly within the bulb of the cryoprobe [7]. This causes cooling of the probe tip to temperatures of −50 to −80 °C [8].

Cryoanalgesia has been reported to be effective on post-thoracotomy pain [8–10], but its efficacy remains uncertain [11]. For example, Miguel et al. [12] reported that cryoanalgesia was not effective against either acute or post-thoracotomy pain. Hence, the role of cryoanalgesia needs to be confirmed.

The conventional pharmacological treatments used for postoperative pain include opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and other drugs. NSAIDs exert their analgesic effects by inhibiting cyclooxygenase (COX), a rate-limiting enzyme that catalyzes the conversion of arachidonic acid to prostaglandins. COX is composed of two isoforms, COX-1 and COX-2, which are constitutively expressed in the spinal cord. In clinical practice, COX-2 inhibitors are widely used for postoperative pain control because they have a similar analgesic effect to NSAIDs, without the gastrointestinal side effects or anti-platelet effects [13, 14]. Other agents, such as pregabalin, were reported to be highly effective for neuralgia associated with the intercostal damage after thoracotomy [15].

Among the NSAIDs, parecoxib (Pfizer, Paris, France) is the first parenteral COX-2 inhibitor available for postoperative IV analgesia in pain management [13]. Parecoxib's peak serum concentrations occur about 30 min after intravenous (IV) administration. Its first perceptible analgesic effect occurs within 7–13 min, with clinically meaningful analgesia demonstrated within 23–39 min, and a peak effect within 2 h following administration of single doses of 40 mg intravenously [16]. The advantages of this analgesic effect include its additive effect with morphine and its morphine-sparing effects [17]. It has been reported that parecoxib is effective for postoperative pain control after various surgeries [18–24].

To date, there have been no reports focusing on a comparison of the analgesic effects between cryoanalgesia and parecoxib. We therefore designed this study to compare the analgesic effects of cryoanalgesia and parecoxib in lung cancer patients after lobectomy, and herein propose a relatively better strategy for analgesia.

Patients and methods

Patients

Data for a total of 178 lung cancer patients awaiting lobectomy by open thoracotomy from December 2008 to December 2012 in our department were collected. The exclusion criteria included: (1) preoperative respiratory dysfunction; (2) poor tolerance of the surgery; (3) presentation of any type of pain, a history of a chronic pain syndrome, narcotic use, psychiatric illness or regular steroid use; (4) previous thoracotomy; (5) previous treatment with preoperative chemotherapy or radiotherapy and (6) refusal to participate in the study. Before surgery, the patients received a systemic physical evaluation, including routine tests, a blood gas analysis, pulmonary function tests, chest X-rays and computed tomography scans. In addition, fiberoptic bronchoscopy was performed to confirm the diagnosis of lung cancer. Moreover, head magnetic resonance imaging, abdominal ultrasound and systemic bone scans were performed to exclude distant metastasis.

The framework of the study was designed to comply with the CONSORT statement [25]. Based on the admission number, all patients were randomly divided into two groups: Group A (intercostal nerve cryoanalgesia, $n = 87$) or Group B (parecoxib, $n = 91$). The same physical therapy and nursing staff carried out all postoperative care. Every patient enrolled signed a written consent form approved by the Medical Ethics Committee of Zhengzhou University, which also approved the study protocol.

Management of surgery and anesthesia

All the operations were open thoracotomies. General anesthesia was performed via tracheal intubation. Posterolateral thoracotomy was performed for either side of the lung. The thoracic cavity was entered via the fifth (upper lobe resection) or sixth (middle and lower lobe resections) intercostal spaces and was opened by electrocautery, which was applied to the upper border of the lower rib. A rib spreader was used, and soft thick gauze was placed between the retractor and both of the cranial and caudal wound edges. Ribs were not usually cut off unless the view needed to be enlarged. One-lung ventilation was utilized for all patients. For Group A, cryoanalgesia was performed to target four intercostal nerves: one at the level of the incision, one each at the levels above and below the incision, and one at the level of the drainage tube that was placed at the end of the operation. Cryoanalgesia was performed on the intercostal nerves about 10 cm from the nerve root. The cryoprobe was placed on each nerve, under direct vision and each nerve received a 90-s application to induce a temperature of about −55 to −65 °C. A 10-s thaw was allowed prior to the removal of the probe to prevent adhesion to the tissues. The chest was closed in routine fashion, with the intercostal drains placed within the anesthetized area. Then, a chest tube was placed in the seventh or eighth intercostal space. At the end of surgery, the chest was closed by the edge closure method using a large, blunt needle with biodegradable

polydioxanone sutures. For Group B, 40 mg of parecoxib was pushed intravenously at this time. No other oral drugs were used, while methods such as massage and attention distraction were employed if patients reported experiencing high levels of pain.

Drain insertions were maintained for 3–5 days, and under special circumstances, such as thoracic cavity infection, consistent pulmonary air leakage or consistent large amounts of drainage fluid, the insertions could last longer. The indication for tube withdrawal was that the amount of the clear drainage fluid in a single day was less than 150–200 ml.

Pain assessment

After the surgery, the degree of chest pain, respiratory function and complications were recorded. Postoperative pain was assessed using the Visual Analog Scale (VAS). The VAS is a measurement instrument used to determine the subjective characteristics or attitudes that cannot be measured directly. It involved a 10-cm horizontal line, with the left end representing 'no discomfort' and the right end representing 'maximum discomfort' (0–10 points) [26]. The scores were recorded for 7 days postoperatively, and patients were followed at regular intervals until 6 months after discharge.

Statistical analysis

All statistical analyses were performed using the SPSS 13.0 software program (SPSS, Inc.). The Chi squared test was used to analyze the qualitative data. The *t* test was used to analyze continuous data. Values of $P < 0.05$ were considered to be significant.

Results

The patient characteristics are presented in Table 1. Because of the high prevalence of bulky tumors and major vessel invasion, the skin incision lengths were larger than the international standard (8–12 cm).

During the first week, the pain scores of Group A were significantly lower than those of Group B on days 1, 2, 3 and 7 ($P < 0.05$). One month after the surgery, the patients in Group A felt no apparent pain and only had local numbness around the incisions, while the patients in Group B still had feelings of persistent pain around the incisions and in the upper abdomen, with a significant difference in the pain scores being present between the two groups at this time ($P < 0.05$). Six months after the surgery, the pain had basically disappeared in all patients in both groups, and there were no significant differences in the pain scores between the two groups ($P > 0.05$) (Fig. 1).

Table 1 The baseline characteristics of the patients

Variable	Cryoanalgesia group	Parecoxib group	*P*
Total patients	87	91	
Sex			
Male	56	59	0.948
Female	31	32	
Age (years)	68.2, 41–78	66.8, 45–77	0.647
PS score			
0	66	68	0.831
1	18	21	
2	3	2	
Tumor location			
Left lung	39	50	0.177
Right lung	48	41	
Stage			
I	9	11	0.843
II	32	30	
III	46	50	
Histology			
Adenocarcinoma	47	54	0.771
Squamous	31	29	
Large cell	9	8	
Skin incision length (cm)	23.2 ± 2.3 (18.2–27.6)	22.5 ± 2.6 (17.5–27.3)	0.537

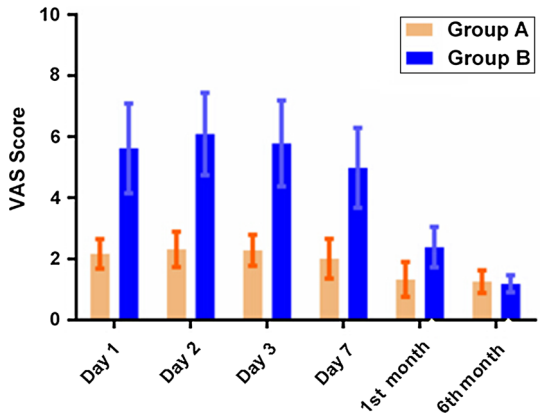

Fig. 1 A comparison of the analgesic effects of cryoanalgesia and parecoxib. The VAS scores were as follows: Day 1: 2.17 ± 0.48 vs. 5.62 ± 1.47, $P < 0.05$; Day 2: 2.32 ± 0.58 vs. 6.09 ± 1.35, $P < 0.05$; Day 3: 2.29 ± 0.51 vs. 5.78 ± 1.41, $P < 0.05$; Day 7: 2.01 ± 0.65 vs. 4.98 ± 1.31; First month: 1.33 ± 0.57 vs. 2.39 ± 0.66; Sixth month: 1.26 ± 0.37 vs. 1.19 ± 0.28, $P > 0.05$

The patients in Group A used significantly less morphine than those in Group B ($t = 1.89$, $P < 0.05$). In Group A, there were two patients who developed pneumonia, one who developed atelectasis, and none had intestinal disturbances. In Group B, four patients developed pneumonia,

Table 2 Comparison of the postoperative complications in the two groups

Group	*n*	Pneumonia (%)	Atelectasis (%)	Intestinal disturbance (%)	Somnolence (%)
A	87	2 (2.30)	1 (1.15)	0 (0)	0 (0)
B	91	4 (4.40)	3 (3.30)	7 (7.69)	4 (4.40)
		$x^2 = 12.14$	$x^2 = 11.56$	–	–
		$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$

three developed atelectasis, seven developed intestinal disturbance and four developed somnolence. All of the differences in each complication between the two groups were significant ($P < 0.05$) (Table 2).

Discussion

In this study, cryoanalgesia was compared with parecoxib in post-lobectomy pain management. Based on the patient-reported postoperative pain scores recorded in both groups within the first 6 months after surgery, cryoanalgesia seemed to have better analgesic effects and resulted in fewer postoperative complications than parecoxib, which means that the patients who received cryoanalgesia enjoyed a better quality of life.

All of the operations performed in the present were open thoracotomies, because the aim of the study was to observe the analgesic effects. Video-assisted thoracic surgery was not applied, because even though patients require anesthesia after surgery, the pain is less intense because the wound is smaller, so the difference in the analgesic effects between the different groups would likely not be insignificant.

In this article, the skin incision lengths were 24 (15–30) cm and 22 (17–28) cm in the two groups. These lengths are similar to the results of other studies of thoracotomies [27]. Accordingly, these results may not be generalizable for patients who receive "internationally standard" thoracotomy (usually, the length size ranged 8–12 cm). Therefore, the present study was performed focusing on patients with "larger-sized" thoracotomy incisions, and these results can be considered to be more suitable for such patients.

Even for controlling the acute post-lobectomy pain, cryoanalgesia also provided better results than parecoxib, because patients with cryoanalgesia needed much less morphine than those treated with parecoxib. However, it should be noted that cryoanalgesia was not able to provide complete pain relief after lobectomy. Some other adjuvant analgesic methods sometimes are still necessary.

Apart from the two methods employed in the present study, a few other methods are presently being applied to relieve post-thoracotomy pain. However, each of these is associated with specific disadvantages and side effects. For example, an intercostal block is time-consuming and usually requires repeated blocks, and also carries a risk of inducing pneumothorax and local anesthetic toxicity. Parenteral opiate administration has been reported to be ineffective in some cases, and is associated with respiratory depression, intestinal disturbance and peripheral vasodilatation. Pregabalin was also reported to be highly effective for neuralgia associated with intercostal damage after thoracotomy [15] but is not routinely used in our hospital so it was not applied in the present study.

Epidural anesthesia, a standard analgesic method used for thoracic surgery, especially with standard thoracotomy [28], was not performed in the present study. Epidural anesthesia is usually used for abdominal surgery and inferior-abdominal surgery, requires skilled anesthetic techniques, and can induce hypotension, urinary retention and motor loss [1, 12]. Moreover, epidural anesthesia is applied more often during operations than after operations. It is not a necessary method for patients undergoing a large-sized thoracotomy, and the two methods applied in our present study are more convenient and practical. However, further studies on the effects of epidural anesthesia and other methods should be performed to provide a comparison with cyroanesthesia.

Several previously reported studies have already compared the use of cryoanalgesia with other forms of post-thoracotomy analgesia, with varying results [9, 29–35]. However, in clinical practice, we found that the intercostal nerve cryoanalgesia could be performed in a short time and provided satisfactory analgesic effects and low rates of postoperative complications. However, there were still a few patients who endured unsatisfactory analgesic effects. Possible reasons for this included a selection of inappropriate sites for cryoanalgesia and/or different temperature requirements. Under these circumstances, drugs like parecoxib might be a better choice.

Our results suggest that cryoanalgesia does not result in permanent neural damage, emphasizing the safety of cryoanalgesia. An animal model has confirmed this conclusion [8]. However, long-term follow-up will be needed to provide data on the long-term patient outcomes.

In conclusion, cryoanalgesia of the intercostal nerves can be considered an economical, safe and simple technique for the long-term control of post-lobectomy pain in NSCLC patients undergoing large-sized thoracotomy. Further investigations with larger sample sizes are necessary to highlight which treatment(s) or combinations of treatments can provide the optimal long-term effects for patients.

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Conflict of interest The authors declare no conflicts of interest.

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