Comparison of non-divided intercostal muscle flap and intercostal nerve cryoanalgesia treatments for post-oesophagectomy neuropathic pain control

Qiang Lu, Yong Han, Wei Cao, Jie Lei, Yi Wan, Fang Zhao, Lijun Huang, and Xiaofei Li

OBJECTIVES: Oesophagectomy is at present considered to be the optimal curative treatment for patients with severe oesophageal disease. Postoperative pain, both acute and chronic, plays a significant role in the quality of life for post-oesophagectomy patients. The present study compared the effects of two methods—application of a non-divided intercostal muscle flap (NIMF) and intercostal nerve cryoanalgesia (INC) treatment—in reducing neuropathic pain in post-oesophagectomy patients.

METHODS: From June 2009 to June 2010, a total of 160 patients who underwent posterolateral thoracotomy and oesophagectomy were subsequently recruited to our study and divided into NIMF and INC groups at random. Patient follow-up studies were conducted for one year on all the subjects and the resultant postoperative pain, chronic pain, rehabilitation and complication scores were measured and documented.

RESULTS: INC treatment was more time-intensive than NIMF treatment (P < 0.05). Also, additional chest tube drainage and subsequent extubation were often necessary in the INC group (P < 0.001). No statistically significant differences were found between the two groups regarding the number of subjects who required oral medication one month postoperative with respect to pain score. The chronic pain level, as well as the number of patients requiring oral pain medication, increased significantly by the sixth month following operation and notably increased until the 12th postoperative month in the INC group (P < 0.05).

CONCLUSIONS: Both NIMF and INC treatments were effective and safe for the treatment of acute pain after oesophagectomy. NIMF was the better technique in reducing chronic postoperative pain.

Keywords: Oesophagectomy • Non-divided intercostal muscle flap • Intercostal nerve cryoanalgesia • Pain score • Postoperative chronic pain

INTRODUCTION

Oesophagectomy is currently considered to be the pre-eminent treatment for patients suffering from severe oesophageal disease, such as oesophageal cancer [1]. Acute and chronic postoperative pain is responsible for both physical and mental suffering in patients undergoing thoracotomy, which may impact the quality of life of these patients in many ways [2].

Though commonly observed, the mechanism by which pain occurs after thoracic surgery is complex and poorly documented. Postoperative pain in patients undergoing thoracotomic surgery may be correlated with diverse factors including the surgical incision, dysfunction of the intercostal nerves, rib fractures, inflammation of the chest wall, pulmonary parenchyma, pleura irritation and intrathoracic drain tubes [3, 4]. Despite these possibilities, the disruption of the intercostal nerve—as a direct result of surgical incision, retraction, intraoperative retractor placement or suture—is considered by contemporary researchers to be the primary cause of observed acute and chronic postoperative pain [5–7]. Thus, therapies targeting the intercostal nerve are often effective at alleviating postoperative pain.

Cryoanalgesia is a safe, simple, inexpensive and rapidly executed method for influencing nerve conduction in the treatment of neuropathic pain [8]. Intercostal nerve cryoanalgesia (INC) has been previously reported as an optimal method for the reduction of acute and chronic postoperative thoracic pain, with few instances of the long-term histological damage observed in more invasive treatments [9–11]. Some current studies have indicated, however, that cryoanalgesia may actually increase the incidence of neuropathic pain or, in some cases, fail altogether to relieve postoperative pain [9, 12–14]. Prepared intercostal muscle flap therapy during thoracotomy—particularly the non-divided
intercostal muscle flap (NIMF)—may more efficiently decrease postoperative pain [5–7]. This method subjects the intercostal nerve to muscular protection from injury. Though the treatment shows promise, the long-term efficacy of NIMF in controlling chronic postoperative pain, compared with established procedures such as INC, is unknown. Further investigation is necessary to highlight which treatment can provide the optimal long-term results for patients.

The present work examines postoperative pain in posterolateral oesophagectomy patients over a 1-year postoperative period. The effects of NIMF and INC treatment on both initial and long-term postoperative pain were investigated.

**MATERIALS AND METHODS**

**Patients and methods**

Analyses of 160 cases of patients with oesophageal disease, undergoing oesophagectomy with posterolateral thoracotomy, were conducted in our department between June 2009 and June 2010. In accordance with the Hospital Ethics Committee, all patients signed written, informed consent forms prior to treatment.

This study group was equally divided into two treatment groups by a computer-generated randomization list drawn up by the statistician: the assistant informed the surgeon of the assignment just prior to the operation (Fig. 1). The NIMF group comprised 80 patients who were treated with a NIMF and edge closure (Figs 2A, 3A and B). The INC group comprised 80 patients treated with INC and edge closure (Figs 2B, 3A and B). Data collectors and statisticians did not take part in surgery during the trial and were blinded to each other’s data. All subjects subsequently underwent postoperative follow-up over the course of one year. The characteristics of each subject are summarized in Table 1.

All patients were familiarized with the pain level measurement procedure on the day prior to their scheduled surgery and informed that chest tubes would be removed when the drainage was less than 50 mL/d for two successive days. Postoperative pain was routinely evaluated using an 11-point numerical pain rating scale (0 [no pain] to 10 [most severe pain]) on days 1 to 7, as well as 1, 3, 6, 9 and 12 months after surgery.

Exclusion criteria included the following: (1) patients who exhibited preoperative respiratory dysfunction; (2) patients who presented any type of pain, a history of chronic pain syndrome, narcotic use, psychiatric illness, or regularly steroid use; (3) patients who had previously been treated with preoperative chemotherapy or radiotherapy; (4) patients declining to participate in the trial and (5) patients with a history of previous thoracotomy.

**NIMF group**

NIMF treatment was performed using cautery instruments at the start of surgery. The sixth NIMF was harvested by use of cautery instrument with the same settings for all patients. Specifically, cautery instruments were used to open the rib periosteum on the surface of the 6th rib and the periosteum was...
removed from the costal groove to the length of the retractor, using a periosteal elevator. A retractor was placed between the two exposed ribs without muscle flap. The intercostal muscle and the neurovascular bundle from the costal groove of the 6th rib were raised with the ultimate goal of protecting the intercostal nerve. The NIMF was suspended under the retractor, as shown in Fig. 2A. In the course of surgery, the chest retractor was opened slowly in order to avoid complications due to rib fracture. On completion of the operation, the rib periosteum was carefully lowered using the cautery instrument, as shown in Figs 2A, 3A and B.

**INC group**

INC treatment was applied at the end of surgery. Prior to closure of the thorax, the 4th, 5th, 6th, 7th and 8th intercostal nerves (one at the level of the incision, two cranial and two caudal) were identified and exposed by peeling off the parietal pleura (Fig. 2B). Under direct vision, the Maiwand cryoprobe, with CO₂ as the cooling agent, was placed on each nerve. Each intercostal nerve received a 90 s application at a temperature of approximately −60°C. The cryoprobe was operated from a Spembly 140 Cryounit. A 10 s thaw was allowed prior to removal of the probe in order to prevent tissue adhesion. The chest was closed using the edge closure method (Figs 2B, 3A and B).

**Surgical management**

Posterolateral thoracotomy, either left or right, was chosen for surgical management. The thoracic cavity was entered through the 6th intercostal space and opened by electrocautery, applied to the upper border of the lower rib. Soft, thick gauze was placed between the retractor and both the cranial and caudal wound edges in order to protect the area. One-lung ventilation was required for all patients. In both treatment groups, anaesthesia was induced with 0.1 μg/kg remifentanil and 6 mg/kg propofol and 0.1 μg/kg/min remifentanil intraoperatively. At the end of surgery, the chest was closed by the edge closure method using a large, blunt needle with biodegradable polydioxanone sutures (PDS-II: Ethicon, Inc, NJ).

During the first three days following the operation, the patients made use of patient-controlled intravenous analgesia (PCIA) (0.01 mg/ml fentanyl citrate + 0.05 mg/ml tropisetron hydrochloride + 0.5 mg/ml flurbiprofen; basal rate 2.5 ml/h: 0.5 ml patient-controlled analgesia (PCA) at a lock time of 15 min) and pethidine (Table 3). Most patients in both groups used oral analgesics by duodenal feeding tube (acetaminophen oxycodone, 5 mg/6 h) in POD 4–7 (Table 3).
Table 2: Rehabilitation and complication in 7 postoperative days

<table>
<thead>
<tr>
<th>Variable</th>
<th>NIMF group (n = 80)</th>
<th>INC group (n = 80)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.25%)</td>
<td>1 (1.25%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Bleeding</td>
<td>5 (6.25%)</td>
<td>7 (8.75%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Wound infection</td>
<td>6 (7.5%)</td>
<td>5 (6.25%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Leakage and empyema</td>
<td>3 (3.75%)</td>
<td>4 (5%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (2.5%)</td>
<td>2 (2.5%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>15 (18.75%)</td>
<td>17 (21.25%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1 (1.25%)</td>
<td>1 (1.25%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Chest tube drainage (ml)</td>
<td>670.1 ± 156.4</td>
<td>778.5 ± 148.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Chest tube extubation (days)</td>
<td>5.1 ± 1.7</td>
<td>7.0 ± 2.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time to ambulation (hours)</td>
<td>18.54 ± 3.21</td>
<td>18.85 ± 4.05</td>
<td>0.60</td>
</tr>
<tr>
<td>Return to normal daily activities (days)</td>
<td>5.3 ± 1.8</td>
<td>5.6 ± 1.3</td>
<td>0.23</td>
</tr>
<tr>
<td>Postoperative FEV1 (% predicted)</td>
<td>69.25 ± 9.1</td>
<td>67.14 ± 9.8</td>
<td>0.21</td>
</tr>
<tr>
<td>Side effects of analgesic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (6.25%)</td>
<td>6 (7.5%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (2.5%)</td>
<td>3 (3.75%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Sedation</td>
<td>3 (3.75%)</td>
<td>4 (5%)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Pain score assessment and follow-up

The degree of chest pain, use of analgesics, respiratory function and complications were recorded for patients during hospitalization. Patients were visited at regular intervals over the course of the first seven postoperative days, generally in the morning before undertaking any daily efforts or being administered analgesics by trained nurses (also operating blind to group distinctions). The entire survey questionnaire was completed by the patient, without assistance or suggestion. Postoperative pain was assessed using the numerical rating scale (NRS) [15]. At 1, 3, 6, 9 and 12 months post-operation, each patient’s pain score and analgesic use were also recorded by a physician.

Statistical analysis

Based on previous studies [6], sample size was calculated to be 75 patients in each group to provide 90% power and 0.05 statistical significance level (α = 0.05, β = 0.1). Data were entered into the computer and statistical analysis was performed with SPSS 16.0 for Windows (SPSS, Inc, Chicago, IL). Comparison of continuous data, such as pain scores, skin incision length, oral medication use and respiratory function, was performed by Student’s t-test and Mann-Whitney U-test. Statistical analysis of qualitative data was performed by Chi-squared test. Statistical significance was set at a P level of less than 0.05 (P < 0.05).

RESULTS

Two hundred and nineteen patients were randomly allocated to this study. We excluded 12 patients from the NIMF group and 14 from the INC group (Fig. 1). The remaining 160 patients were statistically analysed, with 80 patients in each group: 138 patients completed the twelve-month study (NIMF group = 67 and INC group = 71). Seven patients in the NIMF group and five patients in the INC group were not available for follow-up. Six patients in the NIMF group and four patients in the INC group died before the study reached completion (Table 4).

Only 2.3 min were required to perform NIMF treatment, while nearly 8.8 min were required for INC treatment (Table 1, P < 0.05). No variance was observed in the total surgical operating time between the two groups. A total of eight patients in the NIMF group experienced rib fractures during operation, compared with nine in the INC group, demonstrating no statistical significance between the two groups (Table 1, P > 0.05). No significant differences were observed between the two groups in terms of age, sex, diagnosis, skin incision length, rib fracture and side (left or right) of operation (Table 1, P > 0.05).

No significant differences were observed between the two groups in terms of postoperative complications, time to ambulation, return to normal daily activities, postoperative mortality or forced expiratory volume in one second (FEV1) at 1 week (Table 2, P > 0.05). The incidence of side-effects of analgesic treatment, such as nausea, vomiting and sedation, were similar in the two groups (Table 2, P > 0.05). Compared with the NIMF group, the INC group patients exhibited increased chest tube drainage and extubation (Table 2, P < 0.001).

One death in the NIMF group occurred during postoperative day 5, due to anastomotic leakage caused by the oesophagectomy. One death occurred in the INC group at postoperative day 7, due to pneumonia and multiple organ failure (Table 2).

No statistically significant differences were found between the two groups with respect to postoperative pain score and the number of analgesic doses administered during the first postoperative week. The majority of patients in both groups, whose analgesic effect was not satisfactory, received pethidine for pain relief during the first three postoperative days, while receiving acetaminophen oxycodone from days 4 to 7 (Table 3, P > 0.05). The average pethidine dose was 50 (25.5–75.5) mg/d. The average acetaminophen oxycodone dose was 20 mg/d. Both methods appeared to be effective on postoperative patients.

Although observed levels of coughing varied, the incidence of chronic pain in both groups remained around 20% at 1 month and 10% at 3 months post-operation. No significant difference...
was observed in the number of patients exhibiting chronic pain within 3 months of the operation (Table 4, Fig. 4A, *P > 0.05*). The incidence of chronic pain was increased at month 6 post-operation in the INC group, with statistically significant variances noted between groups at months 6, 9 and 12 (Table 4, Fig. 4A, *P < 0.05*). Consistent with oral pain medicine usage observations, more patients in the INC group required medication to relieve chronic pain. This trend resulted in a medication usage rate of 24% in the INC group by month 12 (Table 4, Fig. 4B, *P < 0.05*).

Common patient complaints included numbness around the incision site during the first 12 months (Table 4, Fig. 4C, *P < 0.05*). Additionally, 22 patients in the NIMF group and 24 patients in the INC group complained of discomfort during intermittent cutaneous stimulation within the first six months following surgery, although these symptoms had generally disappeared entirely by month 9 (Table 4, Fig. 4D, *P > 0.05*).

**DISCUSSION**

Acute and chronic postoperative neuropathic pains are the cause of significant physical and mental suffering in postoperative patients, generally reducing their overall quality of life [2, 16-18]. Acute postoperative pain increases the stress caused by the functions of breathing and coughing, forming a causative factor in postoperative complications such as atelectasis, hypoxemia, pneumonia and respiratory insufficiency subsequent to thoracotomy [19]. Based on these findings, early postoperative pain control may reduce post-oesophagectomy complications and speed overall patient recovery [20]. Many treatment methods are currently used in clinical settings to relieve postoperative pain, including nerve sectioning, phenol ablation, intercostal blocks, intravenous analgesia and parenteral opiate administration. Due to variations in severity and complexity of
side effects, some of these methods have become more prominent in clinical usage, though further study is required to fully identify and establish effective standards for selection of treatment method [18, 21, 22].

Postoperative pain decreases the quality of life for post-oesophagectomy patients. The present study examined INC and NIMF methods for the treatment of intercostal nerve pain. For reasons of easy leakage after operation, we excluded patients who had received prior chemo- or radiochemotherapy. Based on patient-reported postoperative pain scores recorded in both treatment groups within the three initial postoperative months, both methods were proven to be safe and effective alternatives for reducing acute postoperative pain.

Similar postoperative complications, such as bleeding, wound infection, leakage and empyema, atrial arrhythmia and pneumonia, occurred in limited numbers in both treatment groups. No significant differences were observed in the occurrence or severity of postoperative complications and the time until the patient resumed normal activities remained consistent for both the INC and NIMF groups. More chest tube drainage and subsequent extubation were, however, observed in patients who had received INC treatment, suggesting that NIMF may generally be considered as a preferred choice, in consideration of a notable reduction in hospitalization time due to less need for emergency extubation. Additionally, INC treatment generally took up to four times as long to perform as NIMF treatment, as five intercostal nerves must be isolated and individually frozen prior to the end of surgery, whereas significantly less time is needed to prepare the non-divided intercostal muscle flap, which occurred at the onset of the NIMF surgical procedure.

Many contemporary research groups have reported the majority of chronic and severe post-oesophagectomy pain symptoms to be associated with nerve dysfunction and damage [11, 17]. In our study, obvious differences have been observed between INC and NIMF treatment, related to the reduction in chronic postoperative pain as well as hospitalization time.

In the INC group, postoperative pain was reduced by 19% and 11%, respectively, at months 1 and 3 post-operation. Chronic postoperative pain, however, increased by 17%, 20% and 24% at months 6, 9 and 12, respectively. For many patients, standard chronic pain control regimes failed to satisfactorily resolve pain and additional oral medications were necessary. Postoperative pain was generally relieved satisfactorily within 3 months following surgery although, over the duration of treatment, pain was often a chronic issue.

The NIMF group exhibited a significantly lower patient-reported pain score than the INC group at only 6 months post-operation. In the NIMF group, the intercostal muscle flap was harvested on the cranial side of the thoracotomy, near the location of the intercostal nerve. The muscle flap extends the length of the chest retractor blades, freeing the intercostal nerve from the crushing force of the retractor. In order to protect the intercostal nerve on the caudal side—and to provide a greater chance for avoidance of the appearance of small holes in the ribs, as reported by Cerfolio—the edge closure method was used to close the chest after the operation [7]. The results of the current study indicate that nerves and vessels were successfully preserved in both the INC and NIMF treatment methods.

The results of the present study suggest that, although both NIMF and INC provide rapid, safe and effective methods for decreasing acute pain after oesophagectomy, the NIMF method...
may be more efficacious in reducing chronic postoperative pain in oesophagectomy patients.

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REFERENCES


