Control of post-thoracotomy pain by transcutaneous electrical nerve stimulation: effect on serum cytokine levels, visual analogue scale, pulmonary function and medication

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Received 9 June 2011; received in revised form 1 August 2011; accepted 8 August 2011

Abstract

OBJECTIVES: Transcutaneous electrical nerve stimulation (TENS) has been used to control post-thoracotomy pain with contrasting results. We aimed to assess the efficacy of TENS on post-thoracotomy pain in relation of four criterion measurements as: (i) cytokines; (ii) pain; (iii) respiratory function and (iv) intake of narcotic medication.

METHODS: Between January 2008 and October 2010, 58 patients underwent standard posterolateral thoracotomy for resectable lung cancer. Fifty patients were enrolled in the present study and randomized in two groups: TENS group (25 patients) who received postoperatively TENS for 5 days and placebo group (25 patients) without TENS. In both groups (i) serum cytokines (IL-6, IL-10, TNF-α) were measured by ELISA before surgery and at 6, 12, 24, 48, 72, 96 and 120 postoperative hours (POHs); (ii) at the same POHs, the pain score was measured using visual analogue scale (VAS) ranging from 0 to 10 levels; (iii) respiratory function (FEV 1% and FVC % of predicted value) were valuated on 72, 96 and 120 POHs; (iv) the total intake of narcotic medication given during postoperative period of 5 days was recorded. Repeated measures of analysis of variance assess the difference between two study groups. A value of P< 0.05 was considered statistically significant.

RESULTS: Of the 50 patients enrolled, two patients of TENS group and two patients of the placebo group were lost to follow-up. (i) Serum IL-6 (P= 0.001), IL-10 (P= 0.001) and TNF-α (P= 0.001) levels in TENS group were significantly lower than in the control group; (ii) VAS score in TENS group was significantly lower than in the control group (P< 0.001); (iii) recovery of FEV 1 (P= 0.02) and of FVC (P= 0.02) was statistically better in the TENS group than in control group; (iv) morphine requirement was lower in the TENS group with respect to placebo TENS (P= 0.004). After 48 POHs, no patient required supplementary dose of morphine. TENS group compared with placebo-group presented a significant reduction of non-opioid consumption (P= 0.002).

CONCLUSIONS: TENS is a valuable strategy to alleviate post-thoracotomy pain with reduction of cytokine production and of analgesic consumption, and with positive effects on pulmonary ventilation function.

Keywords: Transcutaneous electrical nerve stimulation · Thoracotomy · Pain · Analgesia · Cytokine levels · Pulmonary function · Medication

INTRODUCTION

Thoracotomy can be one of the most painful types of incision that patients can experience. Pain may inhibit effective coughing, deep breathing and restrict early postoperative mobilization. As a result, lung ventilation and independence self-care may not be optimal with a tendency to lung infection. Furthermore, inadequate acute postoperative pain management may contribute to the development of a chronic post-thoracotomy pain syndrome [1]. Thus, the goal of the clinician is to develop an analgesic regimen that provides effective pain relief and to allow postoperative thoracotomy patients the ability to maintain their functional residual capacity by deep breathing. Effective clearing of secretions with cough and early mobilization can lead to quicker recovery and shorter length of hospital stay [2].

Systemic administration of opioids is the simplest and most common method to provide analgesia for postoperative pain but it may be associated with several undesirable effects, such as respiratory depression, sedation, nausea and vomiting [3].

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but this technique may fail, to be contraindicated or impossible for a variety of reasons [5]. The best results of epidural analgesia are obtained by placing the catheter as close as possible to the dermatomal distribution of pain. This occasionally may be difficult. Catheters placed at distant sites infused with morphine provide analgesia but required a much larger dose.

Epidural analgesia may be associated with complications, including hypotension, and a risk of epidural haematoma and nerve injury. Approximately one-third of patients who receive epidural analgesia commonly report shoulder pain on the side ipsilateral to the incision. The origin of this pain is unclear.

Thus, the belief that epidural analgesia should be routinely used for all thoracotomy patients continues to be a topic of debate [1].

Intercostal and paravertebral nerve block seem to be effective in decreasing postoperative pain but long-term outcomes have been less positive, due to the high incidence of development of neurologic disease such as movement limitation or cerebral confusion and the intake of narcotic medication.

**Patient population**

Between January 2008 and October 2010, 58 patients underwent standard posterolateral thoracotomy for resectable lung cancer. Fifty patients were enrolled in the present study; six patients were excluded because of not meeting criteria inclusion; two patients refused to participate. Patients were randomly divided in two groups: TENS group (25 patients) and placebo TENS group (25 patients). Randomization occurred in the order in which patients were enrolled in the study according to the computer-generated randomization schedule prepared before the start of the study. On the day before the operation, postoperative TENS was discussed with each patient. All patients were advised that the TENS treatment did not preclude the administration of analgesics; in this way, they were specifically instructed to request medication to alleviate pain.

Groups were assumed comparable because they involved similar surgical procedures by the same surgeon within the same period. Both groups of patients received identical anaesthesia with selective one lung ventilation. After the operation, all patients had a standard medication using intravenous (IV) patient control analgesia (PCA) as the following: 5 mg morphine IV bolus at first, followed by 1.2 mg/h which can be maximally delivered by any patient with a 5–10 min lockout period for the first 48 POHs. Ketorolac (administered via an intramuscular route at a dose of 15 mg every 6–8 h) was given when the patient noticed strong pain; if the pain was uncontrollable, an additional dose of intramuscular administration of Pentazocine (30–60 mg) was used.

**Materials and methods**

Study design

It is a prospective randomized uncentre study including series of consecutive patients undergoing standard posterolateral thoracotomy for pulmonary resection.

The subjects were randomly assigned to either an active TENS or placebo TENS group, using a computer-generated randomization sequence. Exclusion criteria were: (i) previous history of chronic pain; (ii) preoperative use of narcotic and/or of TENS; (iii) previous thoracic procedure; (iv) presence of pacemaker; (v) neurologic disease such as movement limitation or cerebral confusion and (vi) other types of incision different from posterolateral thoracotomy.

In all patients, blood samples for the cytokine measurement were drawn preoperatively and at the same postoperative hours (POHs) as the pain measurement. In addition, respiratory function and the intake of narcotic medication at a different time of postoperative course were also recorded. The intergroup differences of the variables were then performed to represent the effectiveness of the TENS treatment.

On the basis of other studies, the sample size calculation was based on the assumption that a 2.5-point difference between TENS group and control group on the visual analogue scale (VAS) scale would be clinically significant. Assuming a standard deviation of 2.25 points, an alpha of 0.05, and a beta of 0.20 (power of 0.80); this analysis indicated that a sample size of at least 14 patients per group was necessary.

Signed informed consent was obtained by all patients and the study was approved by the Ethics Committee of Second University of Naples.

Apparatus and TENS treatment

The TENS units provided an asymmetric square biphasic wave form at a frequency of 80 pulse/s and a pulse width of 250 μs. The placebo TENS units appeared identical to the treatment TENS units, including operating indicator lights and batteries, but did not provide current.

Two standard sterile disposable electrodes (20 × 6 cm) with karaya gum backing were placed on the skin on either dorsal side of the incision ~2 cm away the suture line. The standard incision dressing was not disturbed. The leads exited from the cranial end of the electrodes.

The TENS group adjusted the stimulus intensity until a strong but comfortable tingling sensation was felt, whereas the placebo TENS group was told that the electrical stimulation was silent, producing no sensation. However, in the placebo group the TENS unit also displayed an active indicator light, suggesting to the patient that the unit was active.

After the surgical procedure, the patient was transferred to the post anaesthesia care unit and electrodes were placed. TENS immediately started and were performed at intervals of 4 h each, all with a duration of 30 min in the first 48 POHs. Then, TENS was applied twice daily up to 5 postoperative days.
Two investigators were involved in data collection in this study and were trained to standardize treatment and measurements. Investigator 1 was responsible for the patient evaluation and pain assessment in all subjects. Investigator 2 applied TENS treatment in all patients. Only investigator 2 knew if the subject had received active or placebo TENS therapy. Both investigator 1 and the subject were blinded to the TENS therapy. Further, to minimize investigator bias, the investigator who applied TENS therapy instructed patients to say nothing about their perception to the investigator who was assessing pain intensity.

Criteria measurements

Cytokine. Blood samples were collected from an antecubital vein in intervals as follows: before surgery, at 6, 12, 24, 48, 72, 96 and 120, postoperative hours (POHs). The sample was allowed to stand for 30 min for clotting of blood, followed by centrifugation at 3000 G for 5 min, and then stored in deep refrigeration at −80°C until serum cytokines measurements were performed (pg/ml). Serum cytokines consisting of IL-6, IL-10 and tumour necrosis factor-alpha (TNF-α) were measured by the same technologist using commercially available enzyme-linked immunosorbent assay (ELISA). The technologist was blinded of which patients were in the TENS group.

Pain. The VAS, divided into 11 units from 0 (no pain) to 10 (worst pain imaginable), was used for both groups. When asked, patients must touch a point corresponding to their grade of pain, and this mark indicated the degree of pain on the scale. This question using the scale was asked at 6, 12, 24, 48, 72, 96 and 120 POHs.

Respiratory function. Pulmonary function tests (FVC, FEV1) were performed using Spirolab III, Spirometer (Cosmed®). The best of three efforts, completed with the patient setting sitting on the edge of the bed was used for the analysis. The pulmonary function tests were expressed as a percent of predicted value and performed at 72, 96 and 120 POHs.

Analgesic requirement. The intake of analgesic medication at different times of postoperative course (up to the day 5 after the operation) was recorded for both groups. Side effects as nausea, vomiting, respiratory depression, sedation and pruritus were recorded and were treated by means of appropriate medication.

Statistical analysis

Results are reported as means ± standard deviations (SD) for continuous variables and as percentages for categorical variables. The comparison of the difference between the variables measured at the various postoperative time points in the two study groups (TENS vs. placebo group) was achieved by repeated measures analysis of variance (ANOVA). A value of $P < 0.05$ was considered statistically significant. MedCalc® statistical software was used for statistical analysis.

RESULTS

Of the 50 patients enrolled, 4 patients were lost to follow-up. One patient of TENS group refused to continue the study, while in the other three cases (one of TENS group and two patients of placebo group) it was not possible to complete the measurement of all variables at different time points according to our study design. A study flow diagram according to CONSORT guidelines [9] is reported in Fig. 1. Characteristics of two study groups are summarized in Table 1.

Cytokine

Between TENS and placebo groups, the baseline levels of IL6 (34 ± 5.7 vs. 34 ± 6.6), of IL10 (31 ± 11 vs. 33 ± 6.4) and TNF-α were compared for eligibility (n=58)

<table>
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<td>Air leaks</td>
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</table>

Figure 1: Study the flow diagram according to CONSORT guidelines.
(44 ± 8 vs. 47 ± 14) were similar. The postoperative IL-6 levels measurements in the TENS group were reduced in comparison with those in the placebo TENS group at 6 (285 ± 61 vs. 333 ± 43); 12 (228 ± 41 vs. 269 ± 36); 24 (186 ± 31 vs. 223 ± 30); 48 (149 ± 30 vs. 181 ± 21); 72 (120 ± 20 vs. 141 ± 17); 96 (104 ± 13 vs. 115 ± 14); and 120 (75 ± 11 vs. 87 ± 19) POHs (Fig. 2a). The repeated measures ANOVA showed a P value <0.001.

IL-10 blood levels were lower in TENS group with respect to the placebo TENS group at 6 (198 ± 24 vs. 233 ± 27); 12 (167 ± 20 vs. 194 ± 25); 24 (139 ± 20 vs. 163 ± 25); 48 (111 ± 17 vs. 132 ± 23); 72 (93 ± 13 vs. 108 ± 19); 96 (70 ± 9 vs. 87 ± 14); and 120 (47 ± 12 vs. 57 ± 13) POHs (Fig. 2b). The difference between two study groups was statistically significant (P < 0.001).

The postoperative TNF-α levels measurements in the TENS group were less than in the placebo TENS group at 6 (820 ± 119 vs. 977 ± 141); 12 (742 ± 102 vs. 843 ± 98); 24 (665 ± 78 vs. 731 ± 91); 48 (499 ± 84 vs. 576 ± 83); 72 (396 ± 59 vs. 458 ± 90); 96 (280 ± 71 vs. 348 ± 77); and 120 (58 ± 8 vs. 78 ± 17) POHs (Fig. 2c). The repeated measures ANOVA in two study groups showed a P value <0.001.

Pain

Figure 3 depicts the subjective pain scores for the placebo group vs. the TENS during the postoperative course. The mean pain score of the TENS group was lower with respect to the placebo group at 6 (6.5 ± 0.8 vs. 6.8 ± 0.8); 12 (5.7 ± 0.7 vs. 6.3 ± 0.5); 24 (5.5 ± 0.7 vs. 6.1 ± 0.5); 48 (5.2 ± 0.7 vs. 5.9 ± 0.5); 72 (5 ± 0.7 vs. 5.6 ± 0.4); 96 (4.6 ± 71 vs. 5.5 ± 0.5); and 120 (3.9 ± 8 vs. 4.5 ± 0.7) POHs. The difference of VAS score between the two study groups was statistically significant (P < 0.001).

Respiratory function

The recovery rates of FVC and FEV 1 were better and faster in the TENS group than in the control group. FVC on POHs 72: TENS group 61 ± 7.6 vs. control group 56 ± 72; FVC on POHs 96: TENS group 63 ± 7.2 vs. control group 58 ± 6; FVC on POHs 120: TENS group 66 ± 8.8 vs. control group 60 ± 6.1 (Fig. 4a). The repeated measures ANOVA in two study groups showed a P value of 0.02. FEV 1 on POHs 72: TENS group 62 ± 6.6 vs. control group 57 ± 6.4; FEV 1 on POHs 96: TENS group 64 ± 6.2 vs. control group 59 ± 6.2; FEV 1 on POHs 120: TENS group 67 ± 8 vs. control group 62 ± 5.9 (Fig. 4b). The difference between two study groups was statistically significant (P = 0.02).
Analgesic requirement

Morphine requirement was lower in the TENS group referring to placebo-TENS on postoperative day 1 (8.4 ± 9 vs. 11.7 ± 11), and day 2 (7.8 vs. 12.3 ± 10) (Fig. 5). The difference between the two study groups was statistically significant with a P value of 0.004. After 48POHs, no patient required supplementary dose of morphine. TENS compared with placebo-TENS group presented a reduction of Ketorolac consumption in postoperative day 1 (8.4 ± 9 vs. 11.7 ± 11), 2 (7.8 vs. 12.3 ± 10), 3 (13.6 ± 11 vs. 21.5 ± 9.9), 4 (11.7 ± 8.9 vs. 18.8 ± 10), and 5 (9.1 ± 8.7 vs. 16.2 ± 10) (Fig. 6). The repeated measures ANOVA in the two study groups showed a P value of 0.002.

DISCUSSION

The goal of many treatment programmes is to reduce pain and in this way to increase functional ability. TENS was introduced into clinical practice in 1970 as an adjunct to other pain therapies. The mechanism of action of TENS is still not completely understood. The theory behind the technique of TENS is the gate-control theory of pain as postulated by Melzack and Wall [7]. It was thought that pain was largely transmitted by small unmyelinated C fibres which could be inhibited by the activity of myelinated A fibres. Stimulation of these larger A fibres could close the spinal gating mechanism in the substantia gelatinosa and thus can prevent painful peripheral stimuli from gaining access to higher cortical centres. The release of endorphins and activation of inhibitory reflex areas in the brainstem have been proposed as alternative mechanisms for the effect of transcutaneous stimulation [10,11]. Despite TENS having been used successfully for postoperative pain relief in a variety of surgical procedures, its role in controlling postthoracotomy pain remains controversial.

Benedetti et al. [12] in a study including 324 patients undergoing thoracic surgical procedure of different types reported that TENS was not effective in the posterolateral thoracotomy group, which produced severe pain, but was useful as an adjunct to other medications in other thoracic procedures such as muscle-sparing thoracotomy, sternotomy and videothoracoscopy associated with mild-to-moderate pain.

The results from other studies are mixed. Many of them support the efficacy of TENS in patients undergoing thoracotomy, and others find TENS of little or no value after identical procedures.

Warfield et al. [8] and Erdogan et al. [13] established TENS as efficacious treatment in the release of postthoracotomy pain with significant reduction of pain score and of recovery room stays, and improvement of spirometric respiratory function in
patients treated with TENS with respect to the placebo group. Solak et al. [14] found that TENS provided better pain relief and comfort compared to IV PCA from the fourth postoperative day onwards, and this pain-reducing effect continued for at least two months postoperatively. Stratton and Smith [15] reported that TENS performed after thoracotomy provided a significant improvement of FVC compared to the control group, suggesting that TENS improved chest expansion and mobility in line with data of Liu et al. [16]. Rooney et al. [17] found that the TENS reduced the use of narcotics during postoperative course of patient undergoing thoracotomy with significant difference respect to the control group in the first 24 POHs. In contrast, Stubbing et al. [18] found no benefits in terms of pain relief after thoracotomy. The application of TENS neither decreased the frequency of pain nor did it significantly alter the requirements for analgesia. Yet, there was no significant difference between patients who received TENS respect to patients who did not with respect to changes in peak expiratory flow rate.

Our study is designed to clarify whether TENS is an efficacious strategy in controlling postoperative pain after thoracotomy reduction with the result of reducing postoperative pain intensity and analgesic drug intake, and of obtaining faster recovery function. In addition to the above-mentioned criterion measurements as VAS pain, spirometric respiratory value, and narcotic intake which may be affected by patient’s subjective reports, in the present study we also investigate the blood cytokine levels, not reported before. The goal is to have an objective measure of the value of TENS considering that cytokine plays a pivotal role in the acute-phase inflammatory and immunologic response to surgical trauma.

Our data suggest that in comparison with the placebo group, the TENS group associated with a lesser release of IL 6, IL 10 and TNF-α; the mean values of IL 6, IL 10 and TNF-α at any time point of postoperative course are significantly lower in the TENS group than in the placebo group. The correlation between pain and cytokines has been recently studied. A number of cytokines are released from a variety of immune cells and can induce powerful hyperalgesia. Although, so far, there is no evidence that cytokines affect the excitability of sensory fibres, it is clear that messages can be relayed to the brain through activation of vagal afferents, and cutaneous nerves can be activated by cytokines [19]. The levels of IL 6 and of TNF-α are well known to reflect the degree for surgical trauma because they are markers of inflammatory response. The release of IL 6 in the early postoperative period has been found to be significantly lower in patients undergoing VATS major lung resection for non-small-cell lung cancer (NSCLC) than in those receiving thoracotomy [20]. In our study groups the same thoracotomy approach is performed by the same surgeon, and no differences are found in terms of resection. Thus, the only factor that may explain the attenuated inflammatory cytokine response between the two groups is the use of TENS. However, it remains unclear as to how TENS may reduce the levels of cytokine. Cipriano et al. [21] observe that in patients submitted to different cardiac surgeries, TENS presented beneficial effects not only in postoperative pain, but also in selected pulmonary-mechanical properties and electrical activity of thoracic and girdle muscles. In theory, the positive effects of TENS on local muscle electrical activity may elicit a reduced inflammatory response with subsequent reduction of IL 6, IL 10 and TNF-α, as observed in our case. Yet, TENS may interfere with catecholamine release via a series of changes in the endocrine properties of the muscle itself, which may lead to reduce reuptake of some circulatory regulators including catecholamine themselves. Thus, TENS may inhibit sympathetic system via the blockade of both afferent and efferent neural pathways, and this could partly have affected our results considering that cytokine levels are also regulated by sympathetic system activity. Clinically, we observe that the patients of TENS group have significantly lower VAS score with respect to the control group in any time of the postoperative course. The clinical implication of decrease in incisional pain is due to the significant improvement of spirometric value observed in TENS group compared with patients without. In the TENS group FVC and FEV 1 results decreased from 78 and 79% (preoperative results) to 61 and 62% (at 72 POHs), respectively, while in the placebo TENS group FEV 1 and FVC results decreased from 81 and 82% (preoperative results) to 56 and 57% (at 72 POHs), respectively. However, the declining of the placebo TENS group was more than that of the TENS group. During the following period (until the 5th postoperative day) FVC and FEV 1 results increased progressively, but the increase in the TENS group was more than that in the second group.

If the biological effect of TENS is characterized by the significant reduction of cytokine levels, in postoperative outcome the very powerful result of TENS therapy is the improvement of pain on VAS, and of lung function measures, and the reduction of analgesic consumption.

Significant incisional pain can prevent the most aggressive physiotherapy and the most cooperative for achieving optimum respiratory care. The depression of respiratory function represents an inability to breathe deeply, and cough effectively. This leads to significant alveolar collapse, severe hypoxemia and gross postoperative pulmonary complications. Conversely, pain control obtained with TENS would allow the same patients to tolerate more vigorous physiotherapy and spontaneously to generate more effective cough during the postoperative period, as well as to ambulate in a much more liberal manner.

As a consequence of the clinical effects of TENS therapy, we observed a significant difference of opioid intake in patients who received TENS treatment with respect to the placebo group in the first 48 POHs. Then, TENS treatment is associated with significant reduction of non-opioid intake during the following postoperative course (>48 h). These results are in line with other reports [17], and with animal studies which show that TENS in combination with analgesic medications enhances the analgesic effect requiring a lower analgesic dose to produce the same analgesic effect [22]. Thus, the clinical implication of our data suggest that TENS may be useful to reduce the opioid and non-opioid intake reducing the risk of their side effects such as respiratory depression, platelet dysfunction and gastric mucosa ulceration especially in high-risk patients.

In our study group we observed no complication after TENS treatment. However, it is reported that some patients may experience irritation at the electrode site owing to the adhesive or gel employed. In theory, TENS may inhibit the output of some cardiac pacemakers and the use of opiates preoperatively is known to affect the response to TENS post-operatively [23]. Patients naive to opioids have better results with TENS compared with patients who have previously received opioid analgesia. Thus, criteria of exclusion from our study were the presence of cardiac pacemakers and/or history of opioid use. Despite these side effects, if we consider the risk–benefit ratio, the risk can be extremely low for selected patients.
Our data confirm previous reports regarding the efficacy of TENS in controlling postoperative pain [8,13–17], but they disagree with Stubbing et al. [18]. However, methodological differences among studies may explain the different results. The use of TENS over short time intervals as adopted in the present study, rather than continually, may be advantageous by minimizing accommodation or habituation to TENS. Significant effects of TENS after abdominal surgery and cardiac surgery have been demonstrated in studies in which conventional TENS was applied for short periods (from 10 to 180 min of treatment time) [24]. Thus, lack of habituation to TENS sensation may help explain the different results of our study with respect to Stubbing et al. [18], who applied TENS continuously. A second factor that may explain the conflicting results is the intensity of TENS treatment. In theory, the frequency of TENS may be the decisive factor to reach the full effectiveness of the above-mentioned gating mechanism. High-frequency and low-intensity TENS are assumed to work through segmental pain inhibition process (gate control theory). In contrast, high-frequency and high-intensity TENS are assumed to be effective by the release of endogenous opioids (supraspinal effect). Thus, pulse duration and stimulus intensity may be decisive factors for efficacy. Animal and human studies have shown higher analgesic effect by increasing the stimulus intensity or longer pulse duration [24]. Combining high frequency (80 Hz) with high stimulus intensity (250 µs for 30 min), as occurred in the present study, might act both on segmental as well as on supra-spinal levels of pain inhibition systems and therefore can prohibit larger hypoanalgesic effects.

### Study limitations

Our study presents several limitations as follows. First, in our study population TENS is used as additional analgesic medication. Therefore, our study is unable to reveal whether the application of TENS used as the only pain solution is efficacious to control severe pain as that following thoracotomy. Second, the current study shows that TENS had a greater effect than placebo. We were, however, unable to determine the extent of the placebo effect in the present study as we do not have a ‘no TENS’ control group. Third, pain rating index is assessed by means of VAS scale only at rest. Evaluation of pain intensity during functional respiratory tasks as cough is not performed in the current study but it will be included in future investigation. Fourth, further investigations are certainly warranted to study the other humoral and cellular components of the body inflammatory and immunologic responses such as immunoglobulin and complement levels as well as neutrophil and lymphocyte functions. Fifth, considering the small number of our patients, larger studies are wanted to corroborate our results.

### CONCLUSION

Our preliminary data show the efficacy of TENS in control postoperative pain when used together with PCA as adjunctive therapy and supports its use in patients undergoing thoracotomy in agreement with the conclusion of a recent review of Freynet et al. [25]. It permits greater reduction of the postoperative pain intensity, faster recovery function and decreases analgesic drug intake. Furthermore, TENS treatment is safe, inexpensive and easy to use. We did not observe any side effects; thus, TENS may be particularly useful for patients that have liver or kidney disease considering that analgesic drug are extensively metabolized mainly in the liver and predominantly excreted via the kidney. However, a comprehensive team approach to pain management, involving the surgeon and anaesthesiologist, are vital for minimizing postoperative pain and morbidity and improving patient satisfaction.

### ACKNOWLEDGEMENTS

The authors are indebted to Giuseppe Signoriello for statistical revision, and to Mariela Vasiljeva for English revision of the manuscript. In closure, the authors thank Luigi Maione for his patience in preserving and collecting blood samples.

### Conflict of interest: none declared.

### REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr F. Detterbeck (New Haven, CT, USA): This study is a very nice attempt to address an issue that is certainly an everyday concern for thoracic patients. I am a little bit concerned about a few aspects of the study. First of all, I think that there are potential questions about how blinded the study actually was. I know that you attached a placebo TENS unit to the patients that did not receive TENS stimulation, and yet the patients that did have TENS stimulation were actually aware of the stimulation. It also appears to me that there was more manipulation of the stimulators so that I would imagine that the patients that were actually getting the TENS stimulation knew that they were getting TENS stimulation and the ones that were not, even though the stimulator had a light on and was quasi-active, knew that there was a difference. So I wonder about the psychological effect of that.

On the other hand, I think you should be congratulated that there were a number of objective measures in terms of the cytokines and things that would not likely be affected by psychology, such as the amount of pain the patient perceives in a visual analogue scale.

On the other hand, with the objective measures, I am a little bit surprised that there was a difference. And if I understand this correctly, patients had their operation, four hours after their operation, the TENS stimulation was turned on, and six hours afterwards, the blood tests were obtained, and then beyond that, every four hours afterwards, and two hours later they had further blood tests obtained. I would have thought that most of the cytokines and physiologic derangements would have really happened at the time of the operation and would have been less influenced by an intervention that takes place four hours later. So I am a bit surprised at the amount of difference there.

Finally, I have a simple question that I am not sure that I understood correctly. You said there were no morphine requirements after 48 hours, but I think that was an additional morphine beyond the baseline rate of morphine in the PCA. Is that correct?

And then lastly, I wonder what your next step is with this. I am not sure that we have resolved the controversy. There are some conflicting studies. You have shown a positive effect. Do you have any thoughts about why your study has a positive effect whereas it has been conflicting in other studies, and how do we sort out if there is a unifying theme in the way the TENS was applied in the positive studies versus the negative studies and how can we address that further?

Dr Fiorelli (Naples, Italy): First, for the study design of the present paper, we had discussions with the anaesthesiologists regarding the intensity and frequency of TENS and how we should apply TENS, at short time intervals or continually. We decided to apply TENS at short time intervals rather than continually, to minimise accommodation or habituation to TENS.

The second point was to define the pulse duration and stimulus intensity; low intensity and high frequency or high frequency and low intensity, because it may be a decisive factor for the efficacy of TENS.

High frequency and low intensity TENS are assumed to work through a segmental pain inhibition process (gate control theory). In contrast, low frequency and high intensity TENS are assumed to be effective by the release of endogenous opioids (supraspinal effect). So we decided to apply TENS with a high frequency and low intensity and a high frequency and high intensity, because we supposed that it might act on both segmental as well as on supra-spinal levels of pain inhibition systems. Thus, we applied TENS with high frequency and high intensity conversely to other studies in which the authors performed TENS with low frequency and high intensity. Probably it may explain the difference of our results.

Second, the mechanism by which TENS reduces the concentrations of cytokines is not clear. In the study design of this paper, we decided to measure several cytokines, not reported before, to have an objective response regarding the control of pain because in other studies, the results of TENS in controlling pain was measured with other subjective parameters such as respiratory function, but without biological parameters. Probably TENS reduces the cytokine levels because it acts on the electrical activity of the muscle. The beneficial effects on the muscle then reduces the inflammation response and the concentration of cytokines.

Third, regarding the reduction of cytokines observed in the first 6 hours, we applied TENS with high frequency and high intensity, immediately at the end of operation, and in the early postoperative hours, because, according to our experience, it is most important to stop the pain in the first postoperative hours. If we are able to stop the pain in the early postoperative hours, we will have better results later. Probably it is important to measure the cytokine levels in the blood but also in the chest drainage, considering the local production of cytokines. We hope to present these data at a future congress.

Dr E. Lim (London, UK): At each time point you have confirmed statistical significance for your lower pain scales on a visual analogue scale, but the magnitude of effect seems to be relatively small, somewhere between 0.2 and 1. Do you have any comments about that?

Dr Fiorelli: To assess the difference of VAS score, the Mann-Whitney test was used.

Dr Lim: It is statistically significant but the magnitude of effect is very small.

Dr Fiorelli: Yes, it is very small, but probably it may depend on the patients. Sometimes, we have several problems when explaining to patients how the VAS scale works. Thus, the small difference may be because the patients do not understand very well how the visual analogue scale works.

Dr A. Turna (Istanbul, Turkey): Actually we conducted the study with positive results, which you cited during your presentation. I wonder why you have chosen these three cytokines, because, as you know, cytokines have different properties, different effects. Interleukin-6 and TNF-alpha are inflammatory cytokines, but interleukin-10 is the main cytokine for immuno-suppression inducing Th-2 cells. Why did you choose these cytokines and what is the explanation for the decreased levels of these three different cytokines?

Dr Fiorelli: Regarding the choice of cytokines, before starting this study we performed a review of the literature in order to find what kind of cytokines other authors had shown to be correlated with the pain. We decided to measure Interleukin-6 and tumour necrosis factor alpha, because in other studies which compared pain after thoracotomy and VATS, such cytokines were used as representative of surgical stress with higher reduction after VATS procedure. Yet, we also measured interleukin-10, because there was another paper which compared pain after sternotomy and minimally invasive surgery for a cardiac procedure, and the authors measured interleukin-10 as a pain mediator. In the light of these studies, we decided to use these three cytokines.

Dr J. Fibla (Barcelona, Spain): My question is a methodology issue. How did you measure the VAS scale pain? I mean, who was responsible? Was it you, a nurse, was it written in the Cardex?

Dr Fiorelli: For the visual scale, I collected the data which were detected by a nurse in the first two days when the patients stayed in the intensive care unit. Following this, the trainee in surgery entered the data. Probably, there is a bias because different persons retrieved the data and it may explain the small difference observed regarding the VAS pain scale. Unfortunately, the same person cannot detect the VAS score pain, because the patients stayed in different units of the hospital during their postoperative course.