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Rehabilitation of cancer pain in lung cancer: role of manual therapy

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Abstract

Lung cancer is the most common cancer in the world and pain is its most common symptom. Patients with cancer will often undergo multiple medical interventions and prolonged or repeated hospitalizations, they are vulnerable to an overall decrease in activity. The aim of study conducted at the Center for Physical Medicine and Rehabilitation at the University "G.d'Annunzio" Chieti-Pescara, is to evaluate the impact of neuromuscular manual therapy in reducing pain and disability of upper limb and postural disease after thoracic surgery. Recruited 26 subjects divided into an experimental group that has carried out three sessions of manual therapy after surgery, and a control group. Evaluated at the beginning (T0) and the end of the rehabilitation protocol with the VAS scale (Visual Analogic Scale) and S.P.A.D.I. index (Shoulder Pain and Disability Index). Reduction of the perception of pain by 8.6% (±6.56) and disability in the experimental group decreased by 13.9% (±6.56) compared the control group, showed the effective in reducing post-surgical pain and disability in patients with lung cancer.

Key words: rehabilitation, cancer, manual therapy

Introduction

Lung cancer is the leading cause of death in industrialized countries. The AIRC (Italian Association for Cancer Research) showed that the incidence of lung cancer is the second most common form of cancer in men and third in women. [1] This disease alone accounts for 20 percent of all cancers in males. In recent years, however, a progressive increase among women is recording. The reason is simple: women smoke more and smoking is the leading cause of lung cancer. In Italy it is estimated that about 34,000 new cases of cancer each year in people up to 84 years of age, on average one every three men and a woman every four has a chance to have a diagnosis of cancer during their lifetime average (0-74 years), even taking into account of the increase due to the aging population. In Italy die from lung cancer about 27,500 people a year (about 22,000 men and 5,500 women), representing the leading cause of cancer death in men and the second among women. [2]

According to the latest ISTAT (www.istat.it), cancer mortality decreased by about 2 percent a year, but in the case of lung cancer this reduction affects only men, women deaths increased by 1, 5 per cent. For this reason, more and more research works have focused their interest on the many aspects of this disease through drug treatment than simple surgical and last but not least, the treatment of pain before and after surgical. The reduction of pain is related to recovery of the LDAs in the shortest possible time. In evolutionary path of research and medicine, only in recent years, rehabilitation has played an important role, in particular to the treatment of myofascial chains in order to significantly reduce the pain symptoms, without resorting to the exclusive use of drugs, not free from risks considered the impairment, sometimes systemic of such patients. [3][4]

Conventionally these patients til this day have been treated with rehabilitation projects focused primarily on the treatment of respiratory problems and increase of the cost-diaphragmatic compliance, prevention of post-surgical retraction and aerobic reconditioning, without considering the implications, on the musculoskeletal component of other districts involved in the operative act and cause of pain in the long term.

In this regard, Li WW et al (2004) described muscular alterations to load the shoulder after surgery to thoracotomy.[5]

In 2013 AkiOhmori et al. described as the cause of pain after surgery, particularly after VATS (Video – Assisted Thoracic Surgery), the presence of myofascial syndrome in the supraspinatus and infraspinatus; other authors have emphasized the need to deepen this issue with further studies to assess their implications in the postoperative recovery.[6]

Katz et al show that long-term pain 1.5 years after thoracic surgery was predicted by the intensity of pain within the first day after surgery. Acute postoperative pain was significantly more intense among patients who developed long-term pain compared with pain-free patients. More importantly, it suggests that the acute postoperative myofascial pain among patients who later developed long-term pain may not have been as responsive to morphine and other drugs, a finding consistent with certain other neuropathic pains. [7]

As the growing interest of the research against this problem, the objective of the study carried out at the Department of Thoracic Surgery of the Hospital "Santo Spirito" of Pescara was to compare myofascial treatment effects on myofascial pain after surgery than the more conventional techniques.

Materials and methods

Features of the sample

In this RTC were included patients of both sexes, aged between 30 and 80 years old, with diagnosis of a malignant lung disease operated with thoracic surgery using the VATS method, for the study group A, and the same kind of patients for the control group. The randomized pilot study was approved by the local ethics committee in accordance with the Helsinki Declaration and all subjects involved in the study have been informed about the procedure and the aim of the research and signed the informed consent.

Exclusion criteria for the entire sample studied were:

- Past medical history of surgery of the shoulder;
- Simultaneous presence of severe neurological or orthopedic disorders;
- Concomitant bone fractures;
- Rotator cuff injury;
- Shoulder instability;
- Shoulder dislocations;
- Brachial plexus incurie;
- Bone metastases;
- Osteoarthritis/arthritis.

Prothesis

A total of 26 subjects were recruited.

The first experimental group (Table 1) was composed of 13 patients (23% female and 77% male) with an average age of 65, all operated by the VATS surgical method for lung cancer (of which 76% on the right side and 24% on the left side).

The control group (Table 2) was composed of 13 patients (38% female and 62% male) with an average age of 65, all operated by the VATS surgical method for lung cancer (76% right and 24% left).

The control group did not sustain any manual rehabilitation treatment but only the standard drugs nursing and care for this pathology.

Tab. 1. Caratteristic of group A

Caratteristic of group A	
Number patients	13
Mean age	65
Gender	Male 10 77% Female 3 23%
Chirurgic Side	Right side : 10 – 76% Left side : 3- 24%

The experimental group A has carried out three myofascial therapy treatments on specific areas related to the intra-operative position and the bed position of the patient during the post-operative phase.

Tab. 3. Caratteristic of control group

Caratteristic of control group	
Number patients	13
Mean age	66
Gender	Male. 8 – 62% Female: 5 – 38%
Chirurgic Side	Right side : 10 – 76% Left side : 3 – 24%

Rehabilitation Protocol

In the immediate post-operative phase, the experimental group (A) was referred to three sessions of manual myofascial therapy on specific areas, known as trigger points, in relation to the intra-operative position and the bed position of the patient during the postoperative course.

The anatomical regions treated for the study group A have been selected appropriately in a total number of 6 locations.

The treatment consist of the application of manual stimulations aim for the return of correct afferences to the central nervous system (CNS), they also improve the motility of muscular structures, allowing a rebalancing of the whole body system.

The treatment begins with stimulation of the foot arch evaluating and treating specifically the flexor hallucis, flexor digitorum and the abductor of 5th finger to immediately improve and re-enable the veno-lymphatic plantar pump, to rebalance myofascial dysfunctions of those muscle-connective structures and give the patient the opportunity to keep a better arch support in standing position (Fig.1).

Fig. 1. Plantar fascia treatment

Iliopsoas is the second muscle treated, chosen for its great postural role, its fascial connection with the glenohumeral joint and for the stress caused to this structure by immobility from the position in bed during the postoperative course that cause a shortening and a disfunction of this muscle (Fig.2).

Fig. 2. Iliopsoas muscle treatment

The third treated muscle is the diaphragm: its compliance is crucial to get a proper breathing. At the fascial level its constriction can lead to an alteration of the movement of the glenohumeral joint, furthermore the positioning of drainages, usually between 3 ° and 6 ° rib, can be the cause of the alteration of respiratory patterns (Fig. 3).

Fig. 3. Diaphragm treatment

The fourth selected muscle is the pectoralis minor, one of the most important muscole of the biomechanic of the shoulder. It's one of the muscles that is often symptomatic and dysfunctional in a painful syndrome of the glenohumeral joint. The intraoperative position (position of the swordsman with the arm stretched above his head), and the positioning of drainages alter its lenghtening increasing its intrarotative function (Fig. 4).

Fig. 4. Pectoralis minor treatment

Upper trapezius is the fifth selected, it suffer alterations due to the location of the intra-operative and post operative position in bed, resulting in an alteration of the articulatory dynamics of the glenohumeral joint. The selected patients reported pain sensations on that area and irradiation on the typical topographic area of referred pain. (Fig. 5)

Fig. 5. Upper trapezius treatment

The last selected muscle is levator scapulae. This muscle in altered conditions of the shoulder joint becomes the fulcrum of scapular movement generating pain sensations to the neck region, given its insertion between C2-C4, and the medial border of the scapula. The treatment is necessary to improve the movement and the ROM of the scapula with consequential improvement in all planes of motion of the shoulder.

Statistical analysis

For the statistical analysis is used the Wilcoxon Signed-Rank Test, using the statistical analysis software NCSS. Even if it is usually named as Mann-Whitney test, the non-parametric equivalent of the t Student test for paired data it's due to the Wilcoxon. It represents the non parametric equivalent of the t Student test for indipendents samples, and it should be used in place of this when one of the whatsoever necessary assumptions to this it's violated. The value of the p correspondent represents the chance to casually watch a difference of the measure from the one effectively observed: if this probability it's sufficiently small, we can conclude for a difference of the median observed. Theoretical premise is that:

The two samples included in the study are mutually indipendent and the single observations in the samples are indipent;

The observations are comparable (ex.for every two observations we can establish if they are similar or if one of the two it's bigger then the other).

Results

Study Group

Collected data have been processed and analyzed with the Wilcoxon Signed-Rank Test through statistical software NCSS (attachments).

The Wilcoxon Signed-Rank Test is a nonparametric test, used when is not possible to assume a given form for the distribution of the population and / or in the small sample size (n < 25).

Statistical analysis of outcome measures show that in the experimental group A there was a statistically significant improvement on VAS scale in the evaluation before and after operation. The datas shown a decrease in the level of perceived pain in the post operative course, sign of a greater operating fascial that promotes the recovery and reduces the painful component (tab. 4).

Tab 4. Valuation of VAS score before and after treatment of experimental group A. The W test pariedsample was used to evaluate the statistical significativity.

	Mean difference	95,0% lower limits	95,0% Upper limits	*p value*
VAS PRE–POST	6,31	4,80	7,82	0,001

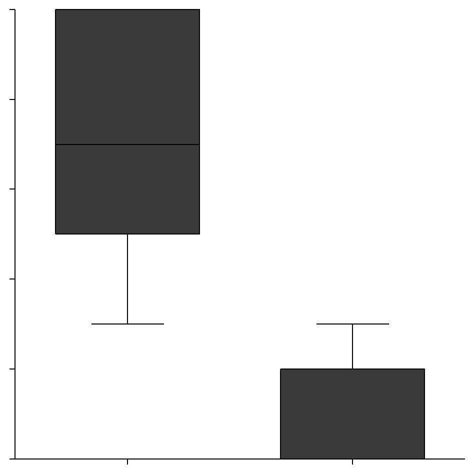
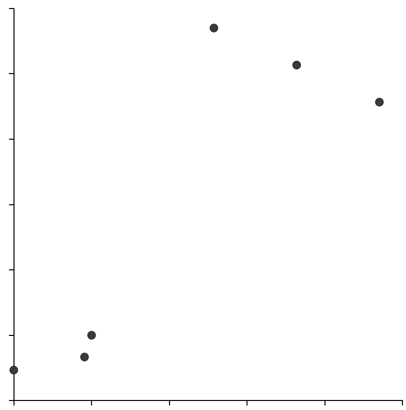


Chart 1. Variation of VAS score in experimental group A

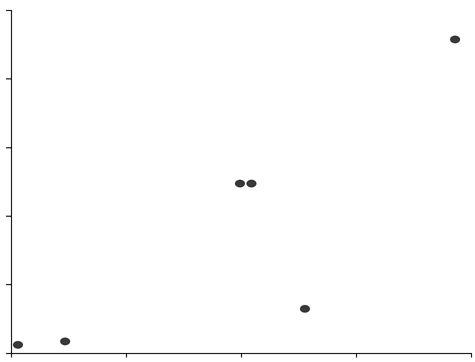
A statistically significant improvement should be noted in the Spadi scale confirming that the myofascial treatment not only reduces pain but also disability, freeing the joint component compromised after the forced position taken during surgery. The change is statistically significant even within the Spadi scale items that were analyzed individually to determine whether there could be differences in the two components of the scales: the pain and disability. (Table 5).

Table 5. Evaluation of pain and disability before and after treatment in the experimental group; was used to assess the statistical significance of these two parameters, the W paried test sample.

	Mean difference	95,0% lower limits	95,0% Upper limits	*p value*
Pain PRE–POST	47,95	36,21	59,68	0,000
Disabilty PRE-POST	47,28	33,66	60,91	0,00001



a) Variation of disability



b) Variation of pain

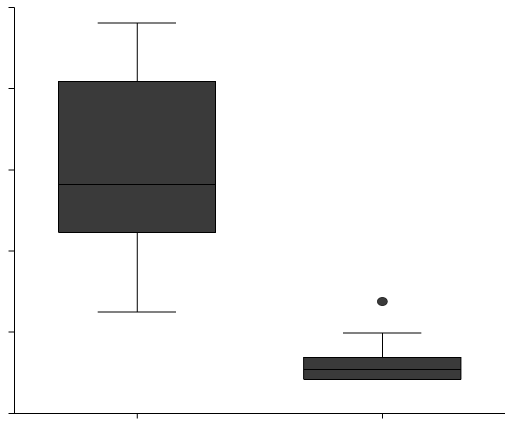
Graphic 2 (a-b). Variation of disability and pain pre e post group A

Score of S.P.A.D.I. scale. Control Group vs Group A with medical care. (tab 6).

The score of S.P.A.D.I. scale was compared with the control group to demonstrate that the differences obtained between the group A and the group that received only medical care and nursing is not due to chance but to myofascial technique chosen for the study (Table 6).

Table 6. Comparison of the total score of Spadi pre and post in the control group and the study group A: has been used to assess the statistical significance of this parameter the W two samples.

	Mean difference	95,0% lower limits	95,0% Upper limits	*p value*
S.P.A.D.I. SCALE PRE-POST	47,58	34,94	60,21	0,001



Graph 3. Comparison of the score change Spadi between the study group A and the control group

Discussion

In the pathogenesis of cancer pain different mechanisms act that accumulate and reinforce each other.

Knowledge of various pathogenic moments that give rise to complex pain syndrome of the cancer patient must be the basis of any analgesic treatment.

Schematically the main components of the pathogenesis of cancer pain are :

a) mechanical stress of soft tissue

The neoplastic invasion causes tissue distension with mechanical stimulation of nociceptors (fascia, periostium, ligaments of the shoulder humeral), reactive inflammation with release of algogenic substances (prostaglandins, histamine) which excite nociceptors and will lower the discharge threshold making them sensitive to even non-noxious stimuli.

Also algogenic afferents originated in injured tissues cause autonomic reflexes that cause vasomotor phenomena (arteriolar spasm and / or vasodilatation) and muscle spasm, resulting therefore in focal and peri focal humoral alterations, This reflex mechanism contributes to a vicious cycle of positive feedback that through secondary tissue alterations exacerbates focal inflammation and the release of substances algogenic.

b) Neurogenic Peripheral Component

The invasion, compression and interruption of nerve trunks by the neoplastic process and post-actinic sclero neoplastic reactive processes, cause a complex peripheral neuropathy.

The ischemic nerve fiber, whose myelin sheath was injured, loses his power of accommodation and becomes hyper excitable, it originates also spontaneously extensive discharge of impulses that cause pain.

If the lesion of the nerve trunk alters especially the conduction of large-diameter fibers occur sensory disturbances and pain resulting from the imbalance of peripheral input.

Also contribute to the genesis of pain spontaneous activity of ganglion cells whose peripheral axons have been cut or injured, and the hyperactivity of neurons of the dorsal horn partially deprived of peripheral in put because of afferent roots lesions.

Also, when a fiber is injured you will have the secondary alterations of its sensory endings that are excited also by chemical stimuli usually inactive.[8] [9][10][11][12]

Cancer pain therefore induces a state of central sensitization, in which neurochemical changes in the spinal cord and forebrain promote an increased transmission of nociceptive information.

Classically, the main emphasis in examining the ascending conduction of pain has been placed on spino-thalamic tract neurons. This means that the general mood and attitude of the patient might also be a significant factor in determining the intensity and degree of pain. [13]

In summary, the nerve and / or root damage causes peripheral alteration of excitability of peripheral receptors, fibers and ganglion cells, with abnormal afferences and imbalanced afferent input, as well as phenomena of denervation, thus resulting in an abnormal afferent message and a spontaneous or induced abnormal activity in the central ways of transmission and conduction of pain. These mechanisms provoke, in cancer patients, the neurogenic peripheral pain: dysesthesia with phenomena of hyperalgesia and tenderness, but also constant continuous, sharp, stabbing, or paroxysmal pain.

In addition to those described schematically other factors may be involved in the genesis of cancer pain:

- Obstruction of the lymphatic vessels, obstruction and spasm of arteries and / or veins by the tumor, lymphangitis and perivascular inflammation causing release of algogenic metabolites, mechanical stimulation of the receptors, autonomic reflexes;
- iatrogenic lesions, such as amputation neuroma, peri- and intra-neural fibrotic and retracting scars, post actinic sclerosis.
- Chemo therapy can induce a toxic poly neuritis that changes the properties of the nerve fiber, causing burning pain, localized dysesthesia in the limbs;
- tumoral and iatrogenic Injuries of the central nervous system,

- Other factors: damage caused b y articular immobilization with myofascial and ligaments syndromes of the affected joints, reflex sympathetic dystrophy; Herpes Zoester, Candida albicans; paraneoplastic syndromes. [14][15]

Breast cancer patients may develop chronic post-surgical pain following breast cancer treatment Risk factors for acute pain and its persistence following breast cancer surgery (Macrae, 2001) [16] and thus adopt specific protective postures resulting in muscle spasm and muscle imbalances (Cheville & Tchou, 2007) [17]. Growing evidence is being produced in support for the use of rehabilithation training in head and neck cancer patients, in order to manage shoulder dysfunction and pain secondary to spinal accessory nerve damage. The importance of correcting posture and scapular stability prior to resistance exercise has been documented by McNeely et al (2004). [18]

The multiplicity of physiopathogenetic factors in play explains why the treatment of cancer pain turns out to be difficult to approach. Also, often the pains occur bilateral and / or in the midline; or, also if pain is abolished in a body part through the use of methods of denervation (neuro lytic block, cordotomy, rhizotomy) the patient perceives another in different site, which had been masked by the more intense and treated with methods aforementioned; or finally anxious and depressed patient continue to perceive pain sensations exacerbated not explicable by etiophysiopathogenesis. For these reasons achieve the reduction of oncological pain symptoms is usually difficult especially if a single method of treatment is used, as stated by the most influential authors in the literature. Typically only a combined multifocal treatment can address the problems of pain therapy of the individual case by resorting to a combination of more than one technique of drug and rehabilitative therapy.

Pain to the omolateral shoulder after torachical surgery it's anguishing, and it alters the respiratory mechanic, the motility and the efficacy of the physical therapy in the post surgical phase (Li WW. Et al, 2004). [5]

The etiology of this pain of the shoulder it's not clear but the scientific community found various possible reasons.

The surgical procedure itself, which rely to the muscular section and the excision of big bronches can induce a pain that is detected by the patient at the gleno-omerular joint level. (Barak M. et al, 2004). [19]

At the same time also the surgical dilatation of ribs and the scapular retraction can cause a stretch of shoulder's ligaments and then produce a painful symptomatology (Mark JB. Et al, 2006). [20]

Some scientifical studies assert that the omolateral shoulder disfunction can be caused by the referred pain of the frenical nerve caused by the irritation of the pleura during the surgical phase or by the toracostomic pipes. (Scawn ND et al, 2011) [21]

Other researchers, instead, argue that the shoulder pain after toracic or abdominal surgery can be a consequence of the diaphragmatical stimulation and it's bound to respiratory (Matsui K et al, 2012). [22]

Even the patient position on the surgical table, in lateral decubitus, with the arm overhead, typical position of the toracotomy, minitoracotomy and VATS surgery, can cause pain to the shoulder and the risk become more intense with the increase of the surgical operation time (Li WW. et al, 2004; Mark JB. et al, 2006).

Finally, the possible implication of the iintervertebral segments motion of the toracic spine should be considered for every problem of the shoulder. Real or potential disfunction, in this region of the spine, can contribute, from a mechanical point of view to the available ROM of the shoulder and, from a physiological point of view, to the pain felt in the shoulder, but referred to all the structures of the toraco-cervical spine. Illnesses in this area usually originate functional limitations of the shoulder, caused by the presence of a neurological reflex arch. The mechanical irritation of the cervical and toracic sympathetic spinal ganglia can exacerbate the sensitiveness of nerves, creating more pain and tenderness to the arm and shoulder (Butler 2000).[23]

The pain felt in the posterior region of the upper arm, it's usually generated at a toraco-cervical level more than at a gleno-omerular level; even the pain felt in the middle area between of the scapula it's usually of toraco-cervical origin. Likewise the pain felt in the supraspinous region of the scapula, without gleno-omerular pain, has probably got a cervical origin.

When pain, paresthesia or dysesthesia are not sgementally distributed (stocking distribution), there is the possibility of a causal relation with the toracical vertebral region, approximately in the junction point beetween the superior third and medial third of the toracical spine.

In all these cases the toracical epidural anesthesia and the farmacological therapy, based on FANS, are considered ineffective for a long-term treatment.

Therefore, it is important to treat the shoulder pain with the best approach, focusing on the multifactorial aetiopathogenesis of pain in this area.

Muscles affected in the long term are the muscles associated with pain and disability yet are not in the direct field of surgery or radiotherapy. Primary muscle shortening and secondary loss of muscle activity may be producing a movement disorder similar to the 'Dropped Shoulder Syndrome'.[24]

Soft tissue mobilisation is widely practised in the management of pain and includes techniques such as scar mobilisation/massage, myofascial techniques and connective tissue massage. A wealth of information is available on such approaches (Hunter, 1994; Mannheim, 2001).

Hirayamaa et al show the efficacy of manual therapy for the alleviation of pain following posterolateral thoracotomy. [25]

According to these, the results show a significant improvement in the group treated with manual therapy study in most aspects of myofascial pain, disability and activities of daily life with the questionnaire Spadi Dysfunction has been described of the fascia as a cause of pain due to a loss of the correct body homeostasis, from this assumption, the neuromuscular manual therapy can be a viable method for the treatment of post-surgical painful shoulder to counteract those compensations that alter functional proper joint mechanics fascial and muscular-skeletal.

Our study, based on the same principle has compared the study group A with the control group highlighting, as shown by the results, a real effect of manual therapy on pain.

Aki Ohmori in 2013 showed how the development of myofascial syndrome of the supraspinatus and infraspinatus muscles as they could create pain and alteration of the movement thus affecting the biomechanics and skeletal muscle.

With this assumption, our study has investigated how the loss of these two important parameters will inevitably lead to increased disability and a decrease of patient autonomy in activities of daily living.

The improvement highlighted by the study group A on Spadi shows that treatment focused on a stimulation, through various manual techniques, of specific trigger points is crucial to the structure to return to its normal function and so setting it again within a dynamic and adapted body balance.

The postoperative pain is a complication that often occurs after a thoracic surgery for lung cancer, is present in 85% of patients who have no symptoms at the time of the transaction. (Mac TB. Et al., 2005) [26]

Bamgbade et al. (2007) found a double etiology of shoulder pain after surgery: this could be a referred pain from the phrenic nerve resulting in irritation of the pleura during surgery itself, or it could be caused by stress on the ligaments of the shoulder following the intra-operative prolonged position.

It is reported that stimulation of specific points on the body surfaces (called "acupoints") during acupuncture therapy could effectively ameliorate the general pain, visceral pain, psychoneurotic disorders, as well as other ailments. [27]

Previous studies reported that acupuncture stimulation induced various physiological changes in the autonomic nervous system, hemodynamics, esophageal sphincter motility, gastric motility, duodenal motility, bladder contraction, secretion of adrenal medullary catecholamines, salivary secretion and others.

These effects of acupuncture were induced by somato-autonomic reflexes or interoceptive-autonomic reflexes through the stimulation of the afferent Aδ- and Cfibers, or afferent group III and IV fibers beneath the acupuncture points. Furthermore, it is reported that the sympathetic nerve ramification activity, innervating the heart, was inhibited by acupuncture stimulation. [28]

The local musculoskeletal disorder possibly causes a continuous activation of local nociceptors that initiates or sustains the central sensitization. Thus, effective manual therapy in acute cases should be able to limit the (time course of) afferent barrage of noxious input to the central nervous system and thus prevent chronicity.

In addition, manual therapy, aimed at improving the motor control in symptomatic regions/joints, is likely to have its importance in the prevention of chronic pain or disfuction. Indeed, a sustained mismatch between the motor activity and the sensory feedback is able to serve as an ongoing source of nociception within the central nervous system.[29][30]

For all this reasons neuromuscular Manual Treatment was effective in reducing post-surgical pain and disability in patients with lung cancer (experimental group A).

Conclusions

The results obtained allow us to hypothesize the introduction of a rehabilitation treatment, consisting of the use of myofascial manual therapy, on specific dysfunctional areas in the post operative period to reduce cancer pain.

This approach could be used in all patients who develop upper-limb pain during post-thoracic surgery, in order to reduce a disturbing element in the recovery process which reduces the respiratory function, promotes accumulation of secretions and It decreases the recovery of patient in the next phase intervention.

In the future it would be desirable and interesting the assessment of ROM joint and vital parameters such as saturation and heart rate in order to establish possible neurovegetative influences. It would be interesting also to evaluate the progress of symptoms comparing this rehabilitative Protocol with different approaches, in order to identify the best possible rehabilitation protocol which is capable of further improving the quality of life of patients in the post operative phase.

Despite the marked improvement of the symptoms of patients undergoing physiotherapy it could be necessary additional studies conducted on bigger samples, in order to formulate scientific evidence with high clinic recommendation strength.

It would also be interesting to increase the number of sample to be taken into consideration and assess data related to the optoelectronic response tonic postural compared to manual treatment.

References:

1. International Agency for Research on Cancer, Monographs on the Evolution of carginogenic risks to humans. Volume 83: Tabocco smoke and involuntary smoking Lyon: International Agency for Research on Cancer (2004)
2. Cancer Facts & Figures American Cancer society 2013 Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845
3. I numeri del cancro in Italia 2014. Available from: http://www.registri tumori.it/PDF/AIOM2014/I_numeri_del_cancro_2014.pdf
4. ISTAT. 100 statistiche per il Paese. Indicatori per conoscere e valutare. 2008.
5. Li WW, Lee TW, Yim AP. Shoulder function after thoracic surgery. Thorac Surg Clin, 2004;14, 331-343.
6. Ohmori A, Hiroshi I. Myofascial Involvement of Supra- and Infraspinatus Muscles Contributes to Ipsilateral Shoulder Pain After Muscle-Sparing Thoracotomy and Video-Assisted Thoracic Surgery. Journal of Cardiothoracic and Vascular Anesthesia, 2013; 1310–1314.
7. Jackson Katz J., Kavanagh Brain P., Sandler AN. Acute Pain after Thoracic Surgery Predicts Long-Term Post-Thoracotomy Pain Clinical journal of pain, 1996 – journals.lww.com
8. Khan IH, McManus KG, McCraith A. Muscle sparing thoracotomy: A biomechanical analysis confirms preservation of muscle strength but no improvement in wound discomfort, Eur J Cardiothorac Surg, 2003; 18: 656-661.
9. Iadarola MJ, Douglass J, Civelli O, Naranjo JR. Differential activation of spinal cord dynorphin and enkephalin neurons during hyperalgesia: evidence using cDNA hybridization. Brain Res.1988;455: 205–212.
10. Peters CM, Ghilardi JR, Keyser CP, Kubota K, Lindsay TH, Luger NM, Mach DB, Schwei MJ, Sevcik MA, Mantyh PW. Tumor-induced injury of primary afferent sensory nerve fibers in bone cancer pain. Exp Neurol. 2005;193(1): 85-100.
11. Patrick W, Clohisy DR, Koltzenburg M, Hunt SP. Molecular mechanisms of cancer pain Nature Reviews Cancer 2002; 2: 201-209.
12. Watkins LR, Goehler LE, Relton J, Brewer MT, Maier SF. Mechanisms of tumor necrosis factor-α (TNF-α) hyperalgesia. Brain Res. 1995; 692: 244–250.
13. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology for Adult Cancer Pain. Fort Washington, PA: National Comprehensive Cancer Network; 2010. [Updated 2010 Nov 1]. Available from: www.nccn. org.
14. Stephani P., Sean P., Edwin W. Chemical mediators of pain due to tissue damage and ischemia. Prog. Brain Res. 2000;129:21–38.
15. Module 1 pain management: pathophysiology of pain and pain management. American Medical Association website. [Updated 2013 Jan 29]. Available from: www.ama-cmeonline.com
16. Katz J, Poleshuck EL, Andrus CH, Hogan LA, Jung BF, Kulick DI, Dworkin RH. Risk factors for acute pain and its persistence following breast cancer surgery. Pain 2005, 119:16
17. Cheville AL, Tchou J. Barriers to rehabilitation following surgery for primary breast cancer. J Surg Oncol. , 2007; 1;95(5): 409-418.
18. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ, 2006;.051-073.
19. Baraka V, Goike H, Panaretakisb KW, Einarssonc R. Clinical utility of cytokeratins as tumor markers. Clinical Biochemistry 2004; 529–540.
20. Allen MS, Darling GE, Pechet TT, Mitchell JD, Herndon JE, Lndreneau RJ, Inculet RI, Jones DR, Meyers BF, Harpole DH, Putnam JB, Rusch VW. The ACOSOG Z0030 Study Group, Morbidity and Mortality of Major Pulmonary Resections in Patients With Early-Stage Lung Cancer: Initial Results of the Randomized, Prospective ACOSOG Z0030 Trial The Annals of Thoracic Surgery Volume 81, 2006; 1013–1020.
21. Scawn ND, Pennefather SH, Soorae A., et al, Ipsilateral shoulder pain after thoracotomy with epidur alanalgesia: The influence of phrenicnerve in filtration with lidocaine, Anesth Analg. 2001, 93: 260-264.
22. Matsui Y, Hiraki T, Gobara H, Uka M., Masaoka Y, Tada A, Toyooka S, Mitsuhashi T, Mimura H, Kanazawa S. Phrenic Nerve Injury after Radiofrequency Ablation of Lung Tumors: Retrospective Evaluation of the Incidence and Risk Factors. Journal of Vascular and Interventional Radiology 2012; 780–785.
23. Doris H, Butler L, Vincent L, Watt–Watson J, Stearns N. Influencing Nurses' Knowledge, Attitudes, and Practice in Cancer Pain Management. Cancer Nursing ; 2000 ; 55-63.

24. Shamley DR, Srinanaganathan R, Weatherall R, Oskrochi R, Watson M, Ostlere S, Sugden E. Changes in shoulder muscle size and activity following treatment for breast cancer Preclinical Study Breast Cancer Research and Treatment 2007; 19-27.

25. Hirayamaa F, Kageyamaa Y, Urabea N, Senjyub H. The effect of postoperative ataralgesia by manual therapy after pulmonary resection. Manual Therapy, 2003 ; 42–45.

26. Mac TB, Girard F, Chouinard P, Boudreault D, Lafontaine ER, Ruel M, Ferraro P, Acetaminophen Decreases Early Post-Thoracotomy Ipsilateral Shoulder Pain in Patients With Thoracic Epidural Analgesia: A Double-Blind Placebo-Controlled Study. Journal of Cardiothoracic and Vascular Anesthesia, 2005; 475–478.

27. Sato A, Sato Y, Schmidt RF. Catecholamine secretion and adrenal nerve activity in response to movements of normal and inflamed knee joints in cats. J Physiol. 1986;375: 611-624.

28. Sato A, Schmidt RF. Spinal and supraspinal components of the reflex discharges into lumbar and thoracic white rami. J Physiol. 1971; 212 Suppl (3): 839-850.

29. Esch T, Guarna M, Bianchi E, Zhu W, Stefano GB. Commonalities in the central nervous system's involvement with complementary medical therapies: limbic morphinergic processes. Med. Sci. Monit. 2004; 10: 6–17.

30. Sakai S, Hori E, Umeno K, Kitabayashi N, Ono T, Nishijo H. Specific acupuncture sensation correlates with EEGs and autonomic changes in human subjects. Evidence-Based Complementary and Alternative Medicine. 2007; 2: 158–169.

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