RESEARCH ARTICLE

Editorial Process: Submission:03/08/2022 Acceptance:10/20/2022

Estimation of Neural Tissue Mobility in Breast Cancer Survivors with Lymphedema

Sandeep Shinde[1]*, Devanshi Joshi[1], Sanjaykumar Patil[2], Piyusha Pawar[1]

Abstract

Background: Lymphedema in breast cancer survivors is a very common condition which progressively may lead to entrapment neuropathy. In lymphedema there is accumulation of fluid due to removal of lymph nodes which causes stretching of nerve fibres within the skin, compression on top of the nerve bundle leading to nerve entrapment. This will increase the neural mechanosensitivity and functional impairment of shoulder as a protective neural response to movement or traction. **Methods:** This study was carried out by assessing the total 72 breast cancer survivor women, with lymphedema. Out of 72, 28 of women underwent lumpectomy, 12 underwent quadrantectomy and 32 underwent unilateral mastectomy. These subjects were assessed for neural tissue mobility by taking pain assessment using visual analogue scale (VAS), range of motion (ROM) using goniometer, lymphedema measurement using an inch tape. The neural tissue mobility for median nerve, ulnar nerve and radial nerve was measured using limb tension test. **Result:** The result obtained from this study showed that neural tissue mobility was significantly impaired in breast cancer survivors with lymphedema. The result of the upper limb tension tests showed 32 women with mild lymphedema had median nerve affected on the involved side 54.1%, about 21 women had moderate lymphedema with 75% of women had median and 25% ulnar nerve affected with median nerve affected in majority of women. Only 19 women with severe lymphedema had all the three nerves affected. **Conclusion:** This study of women who have undergone surgical intervention for breast cancer concludes that there was significant amount of neural tissue impairment noted to mechanical provocation test post operatively after 6 months of surgery. The study suggests that severity of lymphedema was directly related to the nerves affected due to neural tissue impairment.

Keywords: lymphedema- neural tissue impairment- visual Analogue scale- upper limb tension test

Asian Pac J Cancer Prev, **23 (10)**, 3355-3360

Introduction

Breast cancer is most commonly diagnosed and is the leading cause of cancer death among women worldwide (Blecher et al., 2011). It is common in Asian population and with an estimation of 1 in 7 women will develop breast cancer at some time in her life (Loh and Quek, 2011). The incidence of breast cancer (BC) among women has continued to increase within the last decade in spite of screening mammography and the reduction of mortality (Babasaheb et al., 2021). Breast cancer patients are managed with various surgical procedures such as radical mastectomy (RC), modified radical mastectomy (MRM) and breast conserving surgery (BCS) (De GRoef A et al., 2016). Axillary lymph node dissection (ALND), another method is commonly employed as a procedure for diagnosing and treating positive lymph nodes.

However, several consequences may develop after breast surgery, ALND, radiation and chemotherapy, such as axillary web syndrome, frozen shoulder, numbness, shoulder pain and range of motion (ROM) restriction, lymphostasis, and lymphedema (Díaz I et al., 2017). Up to 77% report sensory disturbance in the breast or arm (Smoot B et al., 2014). These short- and long-term consequences have dramatic impact on physical function and quality of life in this population (Norman et al., 2009; Shinde and Patil , 2020; Smoot B et al., 2010).

The lymphatic system has vessels which transport fluid and plasma proteins from interstitial tissue to the blood circulation. When the lymphatic drainage system is impaired draining of lymphatic fluid ceases to work and fluids accumulate in the tissue and therefore lymphedema occurs which may further lead to swelling (Johansson and Branje, 2010). This condition may be reversible and effective treatment includes compression bandaging, wearing a sleeve/glove, manual lymphatic drainage and pneumatic pumping (Johansson and Branje, 2010; Jaju and Shinde, 2019). If the oedema is allowed to progress without treatment the volume will increase, and the arm will get heavy and cause discomfort and pain(Johansson

*[1]Department of Musculoskeletal Sciences, Krishna College of Physiotherapy, Krishna Institute of Medical Sciences, Deemed to Be University, Karad, Maharashtra, India. [2]Department of Obstetrics and Gynaecology,Krishna Institute of Medical Sciences Deemed to Be University, Karad, Maharashtra, India. *For Correspondence: drsandeepshinde24@gmail.com*

and Branje 2010; Casley-Smith JR, 1995). Breast cancer-related lymphedema results from impaired lymph transport due to surgical removal of or radiation-induced damage to axillary lymph nodes and lymphatic channels, which leads to accumulation of lymph in the UE, chest, or trunk (Smoot B et al., 2014).

Neural tissue mobility also called as neuro dynamics which refers to the communication between the different parts of the nervous system and to the nervous system relationship to the musculoskeletal system. Neurodynamic in the sense implied here is the mobilisation of the nervous system as an approach to physical treatment of pain. This mobilisation activates a range of mechanical and physiological responses in nervous tissue such as neural sliding, pressurisation, elongation, tension and changes in intraneural microcirculation, axonal transport, and nervous impulse movements (Shacklock, 1995).

Injuries to the nerve have been reported with axillary dissection which maybe a result of positional tractioning, forceful retraction, direct laceration or contusion of neural tissue during surgery. Nerve injury can also be due to entrapment or compression related to post-operative or radiation-induced fibrosis and scarring (Jare et al., 2019; Shinde 2020; Macdonald et al., 2005). Peripheral nerves when they are subjected to trauma they become "sensitized" less tolerant to the physical stresses (compression and stretch), imposed upon them during movement. The mechanisms responsible for development of neuropathic pain from cancer treatment may also affect the tolerance of the nervous system to movement. Additionally, peripheral nerves at risk during surgery or radiation may be subjected to higher physical stresses during movement due to compression or restrictions from adhesions and fibrosis (Smoot et al., 2014).

There is no such study which shows the impact of lymphedema on neural tissue mobility. So, it is necessary to analyse whether the presence of lymphedema will have an effect on neural tissue mobility which may result in pain, numbness, tingling sensations, restrictions in range of motion of the upper limb while assessing the patient. Adverse neural tension may arise due to inflammation, nerve compression, or impaired blood supply to the area. This study will help add evidences on neural tissue mobility impairment that may happen due to varying severity of lymphedema. Various studies have suggested that neural structures sensitivity is increased due to provocative sequences of upper quadrant movements in in various upper limb pain syndromes. But there are no studies till the date which have assessed for whether the neural tissues become sensitive to such movements following surgery for breast cancer. Soft tissue structures mainly the contractile tissues noncontractile tissues and inert tissues were restricted and compressed during shortening and lengthening. The restrictive and compressive effect of lymphedema resulted in pain, limited mobility of joints as well as restricted neural tissue mobility.

This study was conducted to estimate the changes in pain, upper limb mobility and strength in response to altered upper limb neural tissue mobility and mechano-sensitivity in breast cancer patients with lymphedema.

Materials and Methods

This study was done in a breast cancer survivor support group of Tertiary care hospital in India. The patients who were included in the study had undergone lumpectomy, quadrantectomy and unilateral mastectomy 6 months before entering into this study and suffering from lymphedema. Age group was ranged from 30 to 80 years old women. The subjects excluded from the study were male cancer survivors and patients who have undergone bilateral breast cancer, breast surgery for cosmetic reasons or prophylactic mastectomy, other medical conditions (e.g., arthritis and fibromyalgia syndrome) and recurrent cancer. Before starting the study, all the participants were informed about the study procedure with a written informed consent obtained from each participant. The study was ethically cleared by the Ethical Committee of Krishna Institute of Medical Sciences. Total 72 breast cancer survivor women suffering from lymphedema, who had undergone either lumpectomy, quadrantectomy, unilateral mastectomy 6 months ago and those who are undergoing either radiation therapy, chemotherapy or both were included in this study. The demographic data and past surgical history were taken from subjects prior to the assessment of the condition.

Data Collection Tools

Pain Intensity: An 11-point numerical rating scale (0 = no pain; 10 = maximum pain) was used to assess the intensity of spontaneous neck and shoulder/axillary pain. The patients were asked to not take any analgesics or muscle relaxants 24 hours prior to the assessment.

Range of motion for shoulder was measured by using goniometer. Shoulder movements including flexion, extension, abduction and adduction were assessed.

Measurement of lymphedema was done on the affected upper extremity (usually the one which was operated) and also comparison was done with non-affected side. The lymphedema was measured using an inch tape for segregation of the subjects into mild, moderate, severe lymphedema.

Neural tissue mobility was assessed using the neurodynamic tests for upper limb. ULNTs for the median (ULNT1MEDIAN), Median bias (ULNT2 MEDIAN BIAS), radial (ULNT3 RADIAL), and ulnar nerves (ULNT 4 ULNAR) were performed according to the process described by Butler. (Butler MW, Karagiannopoulos C, Galantino ML, Mastrangelo MA 2019) The patients were in a supine position without a pillow under the head or knees and the legs were uncrossed. The head was in neutral rotation, and the hand of the unaffected arm rested on the side. All the tests were performed on both sides in standardized sequence until the end of range or until the symptoms were reproduced. Before performing the tests, the patients were instructed about communicating the onset of any sensation such as pain or stretch in the areas of the arm and neck. The subject's pain and other symptoms were taken into consideration. The tests were first carried on the unaffected side and then on the affected side. If the patient did not experience pain or any other sensation, the

test was further continued with the elbow extension or the shoulder abduction to the normal end of range. The tests were ceased when the patient experienced, at least some symptoms such as the shoulder girdle attempted to elevate, or when muscular resistance to movement was found.

Statistical analysis

The data collected was statistically analysed using descriptive statistics as mean, percentage and standard deviation. The shoulder mobility of the affected side was analysed and calculated by range of motion. Pain distribution was analysed and calculated using the standard deviation. For lymphedema, girth was measured using an inch tape and analysed by calculating the percentage. The results for upper limb tension test were analysed for radial nerve, median nerve and ulnar nerve.

Results

Participant Characteristics of the Study: The total 72 Women aged between 30-80 years of age had undergone breast surgery and are undergoing either chemotherapy or radiation therapy. Out of 72, 28 (38%) of women underwent lumpectomy, 12 (16%) underwent quadrantectomy and 32 (44%) underwent unilateral mastectomy. The number of women who were taking a combination of radiation and chemotherapy was more 48 (66%) as compared to radiation and chemotherapy alone of 12 (16%) and 16 (22%) respectively. Women between the ages of 41-70 years were the more frequent cases. The participants were the members of breast cancer support group of tertiary care hospital in India.

Pain

The pain in upper limb during activities of daily living was consistent finding in all the participants. The pain assessment was carried out by using VAS scale during rest and during activity. The mean of pain on rest was 0.888+1.056 and during activity was 3.166+2.307. This finding indicate the mild intensity of pain was experienced by the participants during activities of daily living such as bathing or showering, dressing, getting in and out of bed or a chair, walking, using the toilet, and eating. This indicates soft tissue structures mainly the contractile tissues were restricted and compressed during shortening and lengthening. The restrictive and compressive effect of lymphedema resulted in pain.

Shoulder Range of Motion

The shoulder abduction range of motion was limited significantly followed by shoulder external rotation and shoulder flexion. Table 1 shows that Out of 72 women about 57.8% (SD=±10.055) women has flexion limitation, 30% (SD= 5.756) women have extension limitation, 31.5% (SD= 9.936) women have abduction limitation and 20% (SD= 5.828) have adduction limitation. So more number of study participants showed limitations in shoulder flexion, extension and abduction. The shoulder joint movements are limited due primarily by the surgical complications of breast cancer surgeries and secondarily due to the restrictions imposed by lymphedema.

Neural tissue mobility impairments

The neural tissue mobility impairments were directly proportional with the severity of the lymphedema. Table 2 shows neural tissue mobility impairment in breast cancer survivors suffering from lymphedema. Subjects with mild lymphedema, had 48% of neural tissue mobility impairment, with moderate lymphedema, had 32% of neural tissue mobility impairment and with severe lymphedema, had 20% of neural tissue mobility impairment. Neural tissue mobility impairments of the three major nerves of the upper limb were assessed with ULTT and results are showed in Table 4. It showed the involvement of median, ulnar and radial nerve in breast cancer survivors. The result shows that median nerve was more affected in patients suffering from lymphedema 52%, followed by axillary nerve, musculo-cutaneous

Table 1. Range OF Motion of Shoulder Joint

Variables	Flexion	Extension	Abduction	Adduction
Mean	165.55	51.66	133.166	40.944
Percentage	57.80%	30%	31.50%	20%
Standard Deviation	10.055	5.756	9.936	5.828
p value	<0.0001	<0.0001	<0.0001	<0.0001

Table 2. Patients with Neural Tissue Mobility Impairments Suffering from Lymphedema

Category	Percentage of Patients with lymphedema N=72	Percentage of Patients with Neural tissue mobility Impairment N=50
Mild	32 (44.4%)	24 (33.3%)
Moderate	21 (29.1%)	16 (22%)
Severe	19 (26.3%)	10 (13.8%))

Table 3. Neural Tissue Mobility Involvement According to Severity of Lymphedema

TEST	Mild	Moderate	Severe
ULLT 1 (median nerve)	54.10%	50%	50%
ULTT 2 (median nerve, axillary nerve musculocutaneous nerve)	33.30%	25%	20%
ULTT 3 (radial nerve)	0%	0	10%
ULTT 4 (ulnar nerve)	13%	25%	20%

Table 4. Neural Tissue Mobility Involvement According to Severity of Lymphedema

TEST	Mild	Moderate	Severe
ULLT 1 (median nerve)	54.10%	50%	50%
ULTT 2 (median nerve, axillary nerve musculocutaneous nerve)	33.30%	25%	20%
ULTT 3(radial nerve)	0%	0	10%
ULTT 4 (ulnar nerve)	13%	25%	20%

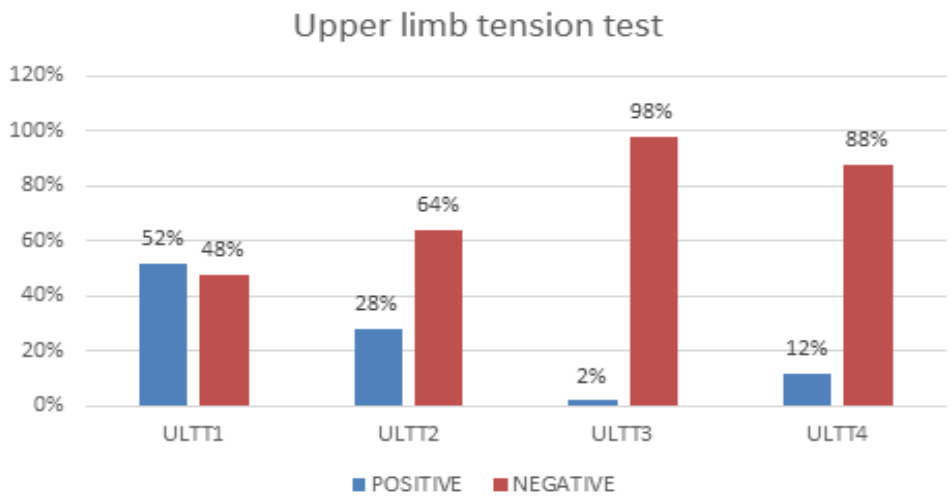

Figure 1. Upper Limb Tension Test

nerve, ulnar nerve and radial nerve. The lymphedema had resulted in significant neural tissue impairments of all the major nerves of the upper limb. The dependent position of upper limb in the erect standing position resulted in the neural tissue impairments of the distal most structures. Mainly the hand and distal forearm were sites for symptoms of compressive neuropathy. The major portion of hand is supplied by the median and ulnar nerves. Table 3. shows that women with mild lymphedema had median nerve affected more on the involved side i.e. 54.1% then ulnar nerve was affected i.e.13% , subjects with moderate lymphedema had 75% of median and 25% of ulnar nerve affected with median nerve affected in majority of women. Also, women with severe lymphedema had all the three nerves affected i.e., median (50%), radial (20%) and ulnar (10%)

Discussion

In this study was focused on the effect of lymphedema in breast cancer survivors on neural tissue mobility. Breast cancer survivors after breast surgery, ALND, radiation and chemotherapy may develop axillary web syndrome, frozen shoulder, numbness, shoulder pain and range of motion restriction, lymphostasis and lymphedema. Up to 77% report sensory disturbance in breast or arm (Smoot et al., 2014).

Many studies report that most cases of lymphedema develop during the first 1-2 years after primary treatment (Schunemann and Willich 1997; Clark, et al., 2005; Kiel and Rademacker 1996). The conducted study interpreted whether lymphedema was present or not, neural tissue mobility persists in most of the breast cancer survivors. Measurement of lymphedema was done on the affected upper extremity (usually the one which was operated) and also comparison was done with non-affected side. Lymphedema was assessed with the help of inch tape and the results were analysed on the basis of mild, moderate and severe. Eleven women had not removed the arm sleeve prior to examination, but eight of them still complied with the definition of lymphedema, so that the procedure violation hardly affected the assessment of lymphedema and also while performing the upper limb tension test.

The result of this study showed that women had more of mild lymphedema (32%). Norman et al., (2009) in their study of lymphedema in breast cancer survivors stated that after breast cancer lymphedema is common but mostly mild type. On self-examination differences observed in hand/arm size and symptoms can be early signs of progressing lymphedema. The results also showed that women who had mild lymphedema were three times more likely to develop moderate or severe lymphedema than women with no lymphedema.

Pain was assessed using Visual Analogue Scale (VAS) for assessing intensity of the neck pain or shoulder or axillary pain. The results showed that pain was experienced more on activity of shoulder and there was relief at rest irrespective of the presence of lymphedema. In Caro-Morán et al., (2014) study of Nerve pressure pain hypersensitivity and upper limb mechanosensitivity in breast cancer survivors it was found bilaterally and widespread nervous hypersensitivity in breast cancer survivors as compared to healthy controls, which were expressed as significantly decreased pressure pain threshold level over the median, radial and ulnar nerve trunks. All the participants in the patient group showed decrease range of flexion and abduction of shoulder. Patient showed mechano-sensitivity in the upper extremity of the affected side as compared to the healthy controls, as demonstrated by a statistically significant reduced range of motion in elbow extension and shoulder abduction during ULNTs for the median, radial and ulnar nerves.

The results of our study showed decrease in range of motion of shoulder flexion and abduction as compared to other movements. Range of motion was assessed using goniometer. Using the VAS pain assessment was taken and it was observed that patients with pain also had restricted range of motion. In some studies, it was stated that the chemotherapy or radiation therapy can cause peripheral neuropathy due to sensory axonal damage, with reduced amplitude of sensory nerve action potentials and changes in afferent activity, leading to widespread pain sensitivity (Wampler, 2006; Wolf, 2008; Argryriou, 2012; Partridge

2004). Smoot et al., in their study of upper extremity impairments in women with or without lymphedema following breast cancer treatment stated that approx. 5-42% of breast cancer survivors develop lymphedema and 47% of have persistent pain.

There are no studies which show the impact of lymphedema on neural tissue mobility. So, it was necessary to analyse whether the presence of lymphedema had an effect on neural tissue mobility which may result in pain, numbness, tingling sensations, restrictions in range of motion of the upper limb while assessing the patient. The result of this study showed that women who were breast cancer survivors had mild lymphedema and had more neural tissue impairment then moderate or severe lymphedema women. The observational studies described an increased neural mechano-sensitivity using the upper limb neurodynamic test 1 (ULNT1) in Breast cancer survivors. This increased neural mechano-sensitivity, may arise after nerve damage and lead to shoulder ROM restriction as a protective neural response to movement or traction. Our study witnessed the reduced range of motion in patients with lymphedema. This states that lymphedema also has an effect on range of motion along with the pain factor. Kelley and Jull (1998), who assessed mechanosensitivity of Upper extremity neural tissue in 20 women with one side breast cancer, before and 6 weeks after Breast cancer surgery found that shoulder abduction ROM during the Upper Limb Tension Test 2 median nerve was reduced on the surgical side.

The upper limb tension test was performed for all the three nerves median, radial and ulnar for assessing the neural tissue mobility in breast cancer survivors. It was observed in our study that the extent of neural tissue mobility impairment was based on the severity of lymphedema and the nerves affected. None of the previous studies shows the extent of neural tissue mobility in relation to lymphedema. One study shows the mechano-sensitivity in women after breast cancer treatment and found significant reductions in elbow extension ROM during ULNTMEDIAN in patients with pain and lymphedema, though the results were not significant in patients with pain but without lymphedema. This study specifically supports the information about which nerve is affected more in patients with lymphedema (Caro-Moran E, et al., 2014).

There were some limitations recognised in this study during the period of study. Range of motion for elbow and wrist are not assessed along with the internal and external rotation of the shoulder joint which can be assessed and noted for future studies. In addition, the study design does not provide information about the possible cause-effect relationship between the lymphedema and the neural tissue mobility impairment. The findings of the current study show the need for rehabilitation programs for the specific treatment of neural tissue mobility impairment in breast cancer survivors and not only targeted to muscular tissue. In view of our results, the health care providers should also look for neural tissue mobility impairments in breast cancer survivors to design rehabilitation programs that take into account the neural component of pain along with lymphedema post-surgical interventions and chemotherapies in this population.

Conclusion

This study of women who have undergone surgical intervention for breast cancer concludes that there was significant amount of neural tissue impairment noted to mechanical provocation test post operatively after 6 months of surgery. The study suggests that severity of lymphedema was directly related to the nerves affected due to neural tissue impairment. Neural tissue mobility impairments should be assessed in women with lymphedema following the treatment of breast cancer. It should be assessed bilaterally for correlation of the symptoms. Therapists need to integrate the findings of neural tissue mobility impairments into the rehabilitation program for breast cancer survivors with pain and lymphedema for better quality of life.

Abbreviations

ALND: Axillary Lymph Node Dissection
ROM: Range of Motion
BC: Breast cancer
ULNT: Upper Limb Neurodynamic Test

Author Contribution Statement

Joshi Devanshi conducted literature review for this manuscript, developed an introduction section of manuscript, conducted the discussion of the study, findings, collected data and analysed the data. Dr. Shinde Sandeep provided a description of the background information, collected data and analysed the data and participated in prescription of the manuscript, all the authors read and approved the final manuscript.

Acknowledgements

We acknowledge the guidance of Dr. S.J. Bhosale. MS surgery and constant support of Dean, Faculty of Physiotherapy, KIMSDU Karad; Dr. Anand Gudur, Department of Oncology, KIMSDU Karad and Dr. Kakade SV, for statistical help.

Ethics approval

The study was approved by institutional ethical committee of Krishna Institute of Medical Sciences Deemed to Be University, Karad, Maharashtra.

Funding Source

This study was funded by Krishna Institute of Medical Sciences Deemed to Be University, Karad, Maharashtra.

Statement conflict of Interest

The authors claimed that there are no conflicts of interest concerning the content of the present study.

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