Manual Therapy as Treatment for Chronic Musculoskeletal Pain in Female Breast Cancer Survivors: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: The purpose of this systematic review was to investigate the effectiveness of manual therapy (MT) for chronic musculoskeletal pain (CMP) in the upper limbs and thorax of female breast cancer survivors and to investigate the changes in the quality of life and function of these patients.

Methods: Systematic searches were performed in the databases MEDLINE/PubMed, Cumulative Index of Nursing and Allied Health/EBSCO, Web of Science, and Physiotherapy Evidence Database, through March 2018, to identify randomized controlled trials investigating whether MT was effective to treat CMP pain in female breast cancer survivors (PROSPERO number CDR42017074175).

Results: The database searches retrieved 1562 titles, and after screening, 5 papers were included for full analysis. The manual therapy techniques described in the included studies involved myofascial induction, myofascial release, classic massage, ischemic compression of trigger points, and myofascial therapy. A meta-analysis, using a fixed-effects model, found that MT decreased CMP intensity (standardized mean difference: 0.32; 95% CI 0.06-0.57), but no significant difference was observed in quality of life after the MT intervention in comparison with a control condition (standardized mean difference: 0.14; 95% CI 0.17-0.46).

Conclusion: Current evidence suggests that MT is considered effective for treating CMP in the upper limbs and thorax of female breast cancer survivors. (J Manipulative Physiol Ther 2019;42:503-513)

Key Indexing Terms: *Breast Neoplasms; Chronic Pain; Musculoskeletal Pain; Musculoskeletal Manipulations*

INTRODUCTION

Breast cancer is the most common type of cancer among women worldwide.[1] The treatments available for breast cancer lead to several known and well-documented consequences such as inflammation and tissue adherence that affect the upper limbs and thorax, leading to physical function impairment and pain.[2,3] Pain becomes chronic and persistent in 60% of cases reported by female breast cancer survivors,[4,5] making chronic musculoskeletal pain (CMP) common after breast cancer.[6]

According to the International Association for the Study of Pain,[7] CMP is a major problem affecting millions of people worldwide. Pain in the shoulder, arm, and thorax embrace the most common physical complaints among women treated for breast cancer, leading to physical impairments and a decrease in quality of life (QOL).[8]

To address CMP from breast cancer treatment, a multidisciplinary approach is proposed, not only to reduce pain complaints and prevent chronicity, but also to improve QOL, because CMP etiology is multifactorial.[9] Hence, rehabilitation programs using stretching, aerobic exercises, strength exercises, and acupuncture have proven benefits for pain reduction.[10] Moreover, manual therapy (MT) seems to provide good results.[11]

In a previous meta-analysis, massage was beneficial for reducing fatigue and negative emotions, although further studies were suggested, addressing QOL and breast cancer–related symptoms[12]; however, massage is only 1 aspect of MT.

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In general, studies suggest that MT has been shown to be an effective treatment option for the relief of musculoskeletal pain in the short term and may be used in combination with other treatments. However, parameters regarding the ideal treatment intensity, application technique, amount of manual contact, and settings are unclear for most treatment options.[13]

In accordance with the American Society of Clinical Oncology Breast Cancer Survivorship Care Guidelines, women with CMP due to breast cancer treatment should receive proper rehabilitation.[10,14] Some treatment options such as stretching, exercises, and acupuncture have been shown to be beneficial for pain reduction in women after breast cancer treatment.[10] Manual therapy has also been shown to have good effects for pain reduction in the same patients.[11] The treatment effects of MT are generally explained by a combination of mechanisms. These explanations include the gate control theory, the biomechanical effects of articular repetitive movement, and the psychological effects of physical contact during the patient-therapist relationship.[15]

Different tissue mobilization techniques used in MT, such as superficial and deep muscle massage, myofascial release, acupressure of trigger points, manual traction, and the mobilization of muscles and articulation,[16] might play an important role during treatment.[11] These maneuvers aim at general relaxation and the release of fibrotic tissue found in muscle and fascia,[17] which produce an increase in the pressure pain threshold, providing analgesia of localized, referred, and general bodily pain, reducing CMP complaints.[16,18]

The literature has highlighted the advantages of MT being a cheap and safe intervention, easy to apply in chronic musculoskeletal conditions.[15] The effectiveness of MT for improving QOL and reducing pain complaints and stress has been described among fibromyalgia patients[19] and for treating shoulder impingement syndrome.[20] Previous studies showed the effectiveness of physical therapy (a combination of MT, active exercise, and strength exercise) for improving impairments in post-breast cancer surgery[21]; however, the benefits of MT on CMP in female breast cancer survivors are not entirely clear.[22]

Considering that breast cancer treatments particularly affect the upper limbs and thorax,[10,23,24] and the lack of consensus in the literature regarding the use and effects of MT to minimize CMP,[11] the purpose of the present systematic review was to investigate the effectiveness of MT as a treatment for CMP in the upper limbs and thorax of female breast cancer survivors. We also analyzed the effects of MT on QOL and function in this same population.

Methods

This study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and was registered at the International Prospective Register of Systematic Reviews (registration number CDR42017074175).

Search Strategy

A systematic search was performed in 4 electronic databases: MEDLINE/PubMed via National Library of Medicine, Cumulative Index of Nursing and Allied Health/EBSCO, Web of Science – Thomson Reuters Scientific, and the Physiotherapy Evidence Database (PEDro) in May 2017, without date and language restriction. A new search was undertaken in March 2018 to update the first search. A manual search was also performed in the reference list of the included articles. The full terms and strategies used are described in Appendix 1.

Study Selection and Eligibility

The selection of studies was undertaken by 2 independent investigators (F.P.S. and G.M.M.). After the database searches were finalized, duplicate articles were excluded. Two investigators verified the eligibility of the selected studies, and a third investigator (K.Z.) was consulted, when necessary, to solve disagreements. Selection was performed first by titles, then by abstract, and finally by full paper. The included articles were read in full by 3 independent reviewers (F.P.S., G.M.M., K.Z.) to verify their content and eligibility.

Articles were eligible if they were randomized clinical trials (RCTs) published in peer-reviewed journals; included women diagnosed with breast cancer who had completed surgical treatment, chemotherapy, and radiation therapy at least 3 months before the MT intervention and had developed CMP in the upper limbs/thorax; with MT as treatment; and CMP as an outcome. Studies were excluded if data from the women were not separately presented in the study and if other cancer types were accepted in the study.

After reading the articles in full, it was unclear whether 3 studies[11,25,26] were referring to chronic pain. Therefore, e-mails were sent to the respective authors, with the aim of obtaining clear information on pain characteristics of the respective studies.

Data Collection and Analysis

Two tables were developed for data collection (Tables 1 and 2) based on Lin et al.[27] Table 1 presents information on the author and year, sample size, intervention received by the experimental group (EG) and control group (CG), and all procedures performed. Table 2 includes data on the instrument used to assess pain, quality of life, shoulder function and other outcomes, and main outcomes.

Two meta-analyses on the effects of MT on pain and quality of life were performed using the software Review Manager 5.3. Data on pain and QOL were pooled and analyzed using standardized mean differences and 95% CIs.

Table 1. *Characteristics of Interventions With Manual Therapy on Chronic Musculoskeletal Pain Among Female Breast Cancer Survivors*

Author/Year	Sample Size	Intervention EG	Procedure EG	Intervention CG	Procedure CG
Castro-Martín et al, 2017[11]	EG: 21 CG: 21	- 1 session of 30 min - Environment-controlled temperature (20°C to 22°C)	- MT intervention with myofascial induction on upper limbs	- 1 placebo session of 30 min (after 4 wk of EG) - Environment-controlled temperature (20°C to 22°C)	- Short-wave pulsed therapy not connected
De Groef et al, 2017[29]	EG: 25 CG: 25	- 24 sessions of physical therapy of 30 min - Twice a week - 12 wk - 12 sessions of myofascial therapy of 30 min each	- Physical therapy: passive shoulder mobilization; pectoralis major stretching; scar tissue massage; exercises for muscular flexibility, resistance, strength, posture, and shoulder active movements - Myofascial therapy: myofascial release on active myofascial trigger points on upper quadrant of body and myofascial adherences on pectoralis, cervical, axilla, diaphragm, and scars	- 24 sessions of physical therapy of 30 min each - Twice a wk - 12 wk - 12 placebo sessions of 30 min each	- Physical therapy: passive shoulder mobilizations; pectoralis major stretching; massage of scar tissue; exercises for muscular flexibility, resistance, strength, posture, and active shoulder movements. - Placebo: positioning of hands on arms and upper trunk, bilateral
Fernández-Lao et al, 2012[25]	EG: 20 CG: 21	- 1 session of 40 min - Environment-controlled temperature (20°C to 22°C)	- Myofascial release on neck area and shoulder (longitudinal strokes, J strokes, suboccipital pressure, frontalis bone spread, ear pull technique)	- 1 placebo session of 40 min (after 3 wk of EG) - Environment-controlled temperature (20°C to 22°C)	- Educational session (nutrition, relaxation techniques)
Listing et al, 2009[26]	EG: 50 CG: 36	- 10 sessions of 30 min each - Twice a wk - 5-wk	- Classical massage on back, neck, and head (superficial massage: shoulder, paravertebral, around scapula, neck and arm). Deep massage: back muscles, trapezium, sternocleidomastoid, and latissimus dorsi and pectoralis major. Rubbing rhomboids, supraspinatus, elevator scapula, and pectoralis major. Depression of shoulder with hands, release of myofascial trigger points on elevator scapula, rhomboids, and supraspinatus.	- 11 wk	- No intervention - Health care routine
Rangon et al, 2017[28]	EG: 10 CG: 10	- 10 sessions of 50 min each - Twice a wk - 5 wk - 50 min of kinesiotherapy - 90 seconds of ischemic compression	- Conventional kinesiotherapy (neck active stretching, anterior and posterior trunk chain; active mobilization of cervical spine, upper limbs; relaxation). - Bilateral ischemic compression on myofascial trigger points on upper trapezius (moderate pain on NRS).	- 10 sessions of 50 min each twice a wk - 5 wk	- Conventional kinesiotherapy (neck active stretching, anterior and posterior trunk chain; active mobilization of cervical spine, upper limbs; relaxation)

CG, control group; *EG*, experimental group; *MT*, manual therapy; *NRS*, numeric rating scale.

Table 2. *Effects of Manual Therapy on Pain, Quality of Life, and Physical Function for Chronic Musculoskeletal Pain Among Female Breast Cancer Survivors*

Author/Year	Outcome Measure		EG Result (Mean ± SD)	CG Result (Mean ± SD)
Castro-Martín et al, 2017[11]	Primary	Pain: pain intensity (VAS)	Pre: 4.90 ± 2.62 Post: 2.62 ± 2.42	Pre: 3.95 ± 2.01 Post: 2.95 ± 2.22
	Secondary	Shoulder function: shoulder ROM (goniometry)	GF: pre: 135.50 ± 25.52; post: 147.52 ± 26.89 GA: pre: 103.67 ± 23.55; post: 127.83 ± 28.42 GER: pre: 58.76 ± 26.11; post: 70.55 ± 22.58 GIR: pre: 69.45 ± 17.72; post: 80.02 ± 12.40	GF: pre: 139.69 ± 20.96; post: 137.21 ± 21.52 GA: pre: 107.00 ± 22.13; post: 106.59 ± 23.64 GER: pre: 60.02 ± 23.63; post: 62.74 ± 23.25 GIR: pre: 70.50 ± 15.29; post: 71.93 ± 14.50
	Other outcomes	Anxiety: anxiety intensity (VAS)	Pre: 4.00 ± 2.19 Post: 1.81 ± 2.16	Pre: 3.52 ± 2.71 Post: 1.95 ± 2.27
		Mood: mood state (Total POMS)	Pre: -16780.95 ± 4576.53 Post: -14733.33 ± 4127.75	Pre: -17423.81 ± 4917.10 Post: -15447.62 ± 4206.26
De Groef et al, 2017[29]	Primary	Pain: pain intensity (VAS)	Pre: 6.7 ± 1.5 Post: 2.3 ± 3.0	Pre: 6.4 ± 1.6 Post: 4.0 ± 3.6
	Secondary	Quality of life: general quality of life (36-Item Short Form Survey)	SF-36 (physical functioning): Pre: 55 ± 24; post: 54 ± 25 SF-36 (mental functioning): Pre: 59 ± 19; post: 62 ± 18	SF-36 (physical functioning): Pre: 54 ± 24; post: 63 ± 22 SF-36 (mental functioning): Pre: 65 ± 16; post: 70 ± 17
		Shoulder function: upper-extremity disability and symptoms (DASH)	Pre: 36 ± 16 Post: 30 ± 17	Pre: 40 ± 19 Post: 33 ± 21
Fernández-Lao et al, 2012[25]	Primary	Pain: pain threshold (pressure electronic algometer [kg/cm^2])	Pre: 2.08 ± 0.74 Post: 2.19 ± 0.65	Pre: 1.92 ± 0.59 Post: 1.97 ± 0.5
	Secondary	-	-	-
	Other outcomes	Immune system: Salivary flow rate (mL/min); α-amylase activity (U/min); Cortisol concentration (μg/ min); IgA concentration (mg/min)	Salivary flow rate: Pre:1.2 ± 0.5; post: 1.5 ± 0.5 α-amylase activity: Pre: 162.1 ± 79.0; post: 287.7 ± 162.2 Cortisol concentration:	Salivary flow rate: Pre:1.3 ± 0.5; post: 1.3 ± 0.5 α-amylase activity: Pre: 159.9 ± 85.1; post: 225.3 ± 106.3 Cortisol concentration:

		(saliva sample)	Pre: 0.3 ± 0.1; post: 0.2 ± 0.2 IgA concentration: Pre: 15.5 ± 7.2; post: 21.8 ± 12.8	Pre: 0.3 ± 0.2; post: 0.2 ± 0.1 IgA concentration: Pre: 16.5 ± 7.5; post: 19.1 ± 10.2
Listing et al, 2009[26]	Primary	Pain: Bodily pain (SF-8)	Pre: 45.6 ± 9.5; post: 49.7 ± 9.1 Follow-up: 49.2 ± 9.0	Pre: 47.8 ± 9.5; post: 44.4 ± 8.6 Follow-up: 45.4 ± 8.0
		Pain: Pain of limbs (GBB)	Pre: 46.4 ± 22.4; post: 37.9 ± 22.8 Follow-up: 39.8 ± 22.0	Pre: 43.3 ± 21.5; post: 42.8 ± 23.0 Follow-up: 39.9 ± 22.5
	Secondary	Quality of life: arm and breast symptoms (EORTC QLQ-BR23)	Breast symptoms: Pre: 25.2 ± 22.6; post: 19.3 ± 21.3 Follow-up: 22.1 ± 19.1 Arm symptoms: Pre: 36.1 ± 27.2; post: 30.6 ± 25.4 Follow-up: 32.1 ± 25.1	Breast symptoms: Pre: 36.1 ± 27.2; post: 28.7 ± 24.5 Follow-up: 31.9 ± 23.5 Arm symptoms: Pre: 34.9 ± 28.2; post: 30.5 ± 25.5 Follow-up: 31.4 ± 20.6
Rangon et al, 2017[28]	Primary	Pain: Pressure pain threshold (pressure electronic algometer- kg/cm^2)	Pre: 1.18 ± 0.47; post: 1.80 ± 0.74	Pre: 1.24 ± 0.67; post: 1.62 ± 0.74
		Pain: Pain intensity (NRS)	Pre: 7.80 ± 1.54; post: 4.40 ± 2.87	Pre: 8.50 ± 1.43; post: 6.00 ± 2.16
		Pain: Pain catastrophizing (PRSS)	Pre: 1.75 ± 1.65; post: 1.40 ± 1.63	Pre: 1.50 ± 1.18; post: 0.82 ± 0.86
	Secondary	Quality of life: breast cancer-specific quality of life (FACT-B+4)	Pre: 109.28 ± 16.58 Post: 102.78 ± 24.39	Pre: 99.71 ± 27.39 Post: 106.59 ± 24.69
	Other outcomes	Temperature: skin temperature (infrared thermography)	Pre: 31.64 ± 1.09 Post: 31.84 ± 1.00	Pre: 31.97 ± 1.30 Post: 31.38 ± 0.92

Note. All results refer to the affected side of the women.

ATOM, Overall Patient Attitudes Toward Massage; *BSF*, Mood Questionnaire of Hecheltjen and Mertensdorf; *CG*, control group; *DASH*, Disability of the Arm, Shoulder and Hand questionnaire; *EG*, experimental group; *EORTC QLQ-BR23*, European Organization of Research and Treatment of Cancer quality of life questionnaire breast module; *FACT-Bþ4*, Functional Assessment of Cancer Therapy-Breast; *GA*, goniometry abduction; *GBB*, Giessen Complaints Inventory; *GER*, goniometry external rotation; *GF*, goniometry flexion; *GIR*, goniometry internal rotation; *NRS*, numeric rating scale; *POMS*, Profile of Mood States; *PRSS*, pain-related self-statement scale; *ROM*, range of motion; *SD*, standard deviation; *SF-8TM*, Short Form-8 Health Survey; *VAS*, visual analog scale.

Table 3. *Methodological Quality Assessment of RCTs—PEDro Checklist*

	Physiotherapy Evidence Database											
Author/Year	(1) *	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	Total
Castro-Martín et al, 2017[11]	+	+	-	+	-	-	-	+	-	+	+	5
Fernández-Lao et al, 2012[25]	+	+	+	+	-	-	+	-	-	+	+	6
Listing et al, 2009[26]	+	+	-	+	-	-	-	-	-	+	+	4
Rangon et al, 2017[28]	+	+	+	+	-	-	+	+	+	+	+	8
De Groef et al, 2017[29]	+	+	+	+	+	-	+	+	+	+	+	9

PEDro, Physiotherapy Evidence Database.

* (1) eligibility; (2) random allocation; (3) concealed allocation; (4) baseline groups; (5) blinding participants; (6) blinding therapists; (7) blinding assessors; (8) proper follow-up; (9) intention to treat analysis; (10) between group comparisons; (11) point measures and variability measures. (+) criteria fully satisfied; (-) criteria not fully satisfied. The item eligibility criteria do not contribute to final score.

The I^2 test was used to analyze the statistical homogeneity between studies, for which a model with fixed effects was chosen, because the I^2 value was less than 25%.

Data on pain were presented in 3 different ways: the visual analog scale (VAS),[11,28,29] pain pressure threshold,[25] and upper limb pain scale Giessen Complaints Inventory.[26] The values for pain pressure threshold post-intervention for Fernández-Lao et al[25] were inverted in relation to the other studies, as these values were inversely proportional to the VAS and Giessen Complaints Inventory upper limb pain scale.

Data on QOL were presented on 3 different scales: general QOL (36-Item Short Form Survey),[29] where the higher the value, the better the QOL; arm and breast symptoms (European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire [EORTC QLQ-BR23]),[26] where the lower the value, the better the QOL; and breast cancer–specific QOL (FACT-B+4),[28] with higher values representing better QOL. Thus, post-intervention values of arm and breast symptoms (EORTC QLQ-BR23) were inverted in relation to the other studies. For the 36-Item Short Form Survey, the values for physical function were used, and for the EORTC QLQ-BR23, the values for the arm symptoms only were used.

Quality Assessment

All RCTs included in the present review were assessed according to the PEDro scale[30] (Table 3), which assesses, through the generation of a score, the risk of bias of each study. The PEDro scale includes 11 items; however, the first item does not add to the final score, so the total score is out of 10. Item 1 assesses whether the study presents clear recruitment and inclusion of participants (external validity), items 2 to 4 are related to selection bias, items 5 and 6 are related to performance bias, items 7 to 9 are related to detection bias, and items 10 and 11 are related to possible bias in the transparency of the results reported (Table 3).[30] The score of each study was retrieved from the PEDro database because all RCTs found in the PEDro are independently assessed by 2 assessors for risk of bias. A score of 1 is attributed if the item is fully satisfied and 0 if the item is not satisfied; an article with a score of at least 6 is considered of good methodological quality.[30]

Results

Studies Included

The database searches retrieved 1562 titles, and no additional articles from reference lists were included. After removing duplicates and screening eligibility by title and abstract, 17 studies were included to be fully read, and 5 studies were included in the present review (Fig 1).

Study Characteristics

Participants were female breast cancer survivors who had completed surgical and adjuvant treatment (eg, radiation therapy and chemotherapy); their age ranged from 25 to 75 years (Table 1). The sample size from the 5 studies combined included 127 women who received treatment (the EG) and 112 who did not receive treatment (the CG).

Mastectomy was the most common treatment received by the included participants, followed by breast-conserving surgery. The average time from surgery to MT intervention varied from less than 1 year[11,26,29] to 17.5 months[28] (Table 1). Two studies included women who were using aromatase inhibitors.[25,29]

Only 1 study[28] reported the period of pain chronicity in detail. On average, chronic pain was present for 23.5 months before the MT intervention in the EG, and 33 months in the CG. Not all studies reported how long women had experienced CMP (Table 1).

Methodological Quality

The methodological quality of the studies is described in Table 3. According to the PEDro checklist, 3 studies

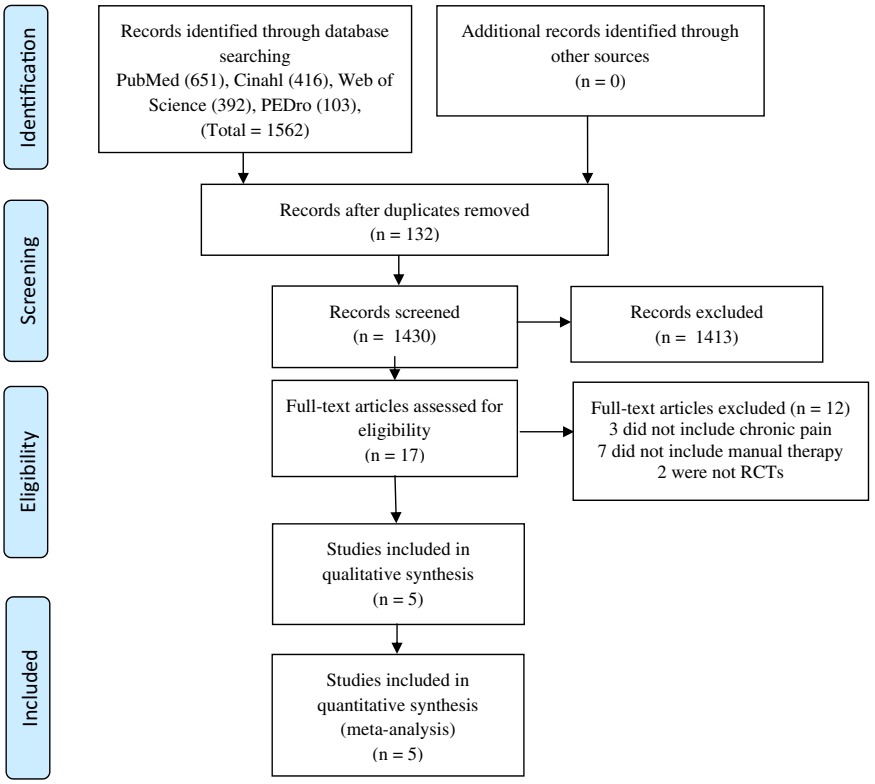

Fig 1. *Flowchart of selected studies retrieved through database searches.* RCT, *randomized clinical trial.*

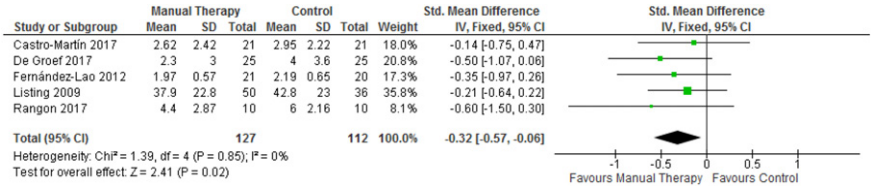

Fig 2. *Meta-analysis comparing manual therapy to a control condition for the outcome chronic musculoskeletal pain in the upper limbs and thorax.* SD, *standard deviation.*

received a score of 6 or more and were therefore considered of good quality. Two studies received a score of less than 6. The highest score among the included studies was 9, which was for the only study that blinded the participants.[29] Considering the difficulties in blinding therapists and patients, we did not expect to include studies with scores of 9 or above, therefore the main issue seen among studies was the lack of control for performance bias (items 5 and 6 of the PEDro scale), followed by lack of control for attrition bias (items 8 and 9 of the PEDro scale).

Intervention

The interventions are described in Table 1. The types of MT used in the studies were myofascial induction,[11] ischemic compression of myofascial trigger points,[28] classical massage,[26] myofascial release,[25] and myofascial therapy.[29]

Outcomes

Primary Outcomes. For the 5 studies included in the present systematic review, CMP intensity decreased, and the pressure pain threshold increased significantly for the EG when compared with the CG after MT. Myofascial release alone did not improve pain sensitivity after only 1 session, when compared to an educational approach.[25]

A meta-analysis with CMP data was performed with 5 studies (Fig 2). Heterogeneity analysis resulted in an I^2 value of 0%, demonstrating no heterogeneity among

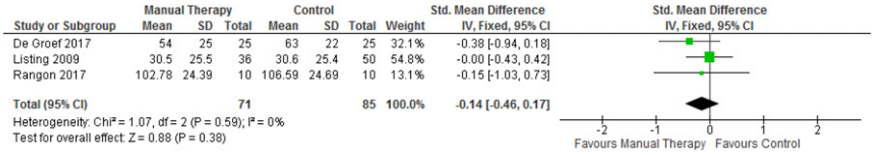

Fig 3. *Meta-analysis comparing manual therapy to a control condition for the outcome quality of life in the upper limbs and thorax.* SD, *standard deviation.*

studies. The standardized mean difference found for the pooled data was -0.32 (95% CI -0.57 to -0.06), favoring the MT intervention in comparison with a control condition.

Secondary Outcomes. Three studies evaluated QOL,[26,28,29] of which none found a significant improvement in QOL after MT. For 1 single case, the CG presented better QOL when compared to the EG.[29]

A meta-analysis with data on QOL was performed with 3 studies (Fig 3). Heterogeneity analysis resulted in an I^2 value of 0%, showing no heterogeneity among studies. The standardized mean difference found for the pooled data was -0.14 (95% CI -0.46 to 0.17), demonstrating no significant difference in QOL after the MT intervention in comparison with a control condition.

Function of the shoulder was analyzed by 2 studies[11,29]; the assessment methods were goniometry[11] and the Disability of the Arm, Shoulder and Hand questionnaire.[29] No differences were found between the EG and CG for shoulder function (Disability of the Arm, Shoulder and Hand questionnaire) in either the short-term or long-term analysis. For goniometry, a significant improvement was found on the operated side for flexion ($F = 25.227$, $P < .001$), abduction ($F = 47.029$, $P < .001$), external rotation ($F = 9198$, $P = .004$), and internal rotation ($F = 12648$, $P = .001$) after the MT intervention.

Other Outcomes. Three studies assessed other outcomes: anxiety intensity,[11] mood state,[11] immunological system with saliva flow rate (mL × min – 1), α-amylase activity (U × min – 1), cortisol concentration (μg × min – 1), IgA concentration (mg × min – 1),[25] and skin temperature.[28]

Only the salivary flow rate improved after MT, with a significant increase for the EG when compared with the CG ($P = .005$); other substances collected by saliva samples presented no differences.[25]

Discussion

The present study investigated the effectiveness of MT in the treatment of CMP among female breast cancer survivors. The results showed that MT decreased CMP in comparison to a control condition, particularly in the meta-analysis, demonstrating a treatment effect of -0.32 (95% CI -0.57 to -0.06) in favor of MT.

All studies showed a positive result in favor of MT, except the study by Fernández-Lao et al.[25] Although the study of Rangon et al[28] had a lower weight in the meta-analysis for CMP (8.1%), it received a PEDro score of 8 and the authors verified that ischemic compression of myofascial trigger points significantly decreased CMP intensity and increased the pressure pain threshold on the affected side of the EG after 10 sessions, in comparison to the CG ($P < .05$).

According to Fernández-Lao et al[31] (PEDro score 6), female breast cancer survivors present a bilateral decreased pressure pain threshold and an increase in pain intensity in the neck (86%), shoulder, and axilla (69%). On average, women with post-mastectomy pain have 5.4 active trigger points in these areas, especially on the pectoral muscles (93%), lower trapezium (79%), and upper trapezium (65%) homolateral to surgery. Manual therapy was shown to be an effective technique to increase the pressure pain threshold in this study.[31]

According to some authors, muscles and fascias become hypertonic and develop points of myofascial strain in women with CMP.[26,32] Some authors explain that MT involving mobilizations can be effective in treating CMP in these patients, as it increases lymphatic and blood flow, tissue nutrition, and oxygen supply to the muscle,[26,32] possibly affecting both superficial and deep tissues. Thus, this technique can possibly assist in the elimination of substance P, lactic acid, and triphosphate adenosine in the areas treated, favoring the decrease in pain sensitivity.[32,33]

In the studies by Hernandez-Reif et al[34] and Hernandez-Reif et al[35] that investigated the effects of MT in 34 women after surgery for breast cancer, MT was performed similarly to the studies included in the present systematic review. The main difference was that the intervention was not local but global, and the CG received progressive muscle relaxation. The authors reported that MT reduced the levels of stress and anxiety in the long term and also increased levels of dopamine and serotonin and the number of NK cells and lymphocytes in breast cancer survivors, decreasing pain levels. These results complement the current review, suggesting that MT applied to the upper limbs and thorax, as well as to the whole body, can potentially decrease CMP.

Fernández-Lao et al[25] (PEDro score 6) reported that decreased pressure pain intensity was not verified after

myofascial release in the short term, although this has limited clinical relevance as it is understood that subsequent sessions could induce long-lasting effects,[11] as observed in other studies that performed a higher number of MT sessions[26,28] included in the present systematic review. For these studies[26,28] 10 MT sessions performed twice a week were sufficient for reducing CMP. The same was observed in the study by De Groef et al[29] after 12 MT sessions twice a week.

The lack of specific information regarding the intensity of strength, tissue resistance, pressure, sliding technique, and hand positioning in the included studies hampers comparisons among studies. A review performed by Zein-Hamoud and Standley[36] studied the manipulative osteopathic maneuvers for tissue repair, regeneration, and inflammation treatment, presenting details of the application, directions, frequency, and length of tissue deformity during MT. The authors suggested that manual techniques require a low load of gentle and painless (3 on VAS) pressure to muscle and fascia over a long period, usually minutes (120 to 300 seconds).[37] However, for breast cancer survivors with CMP, it is not clear whether the suggested parameters promote benefits or are the best option for this population.

The effects of MT for the improvement of CMP are also likely to occur as a result of 3 factors: physiological, biomechanical, and psychological effects. Physiological effects occur after the gate theory,[15] biomechanical effects are a consequence of repeated articular movements, and psychological effects are due to the physical contact that can potentially produce a positive response during the therapist-patient relationship.[15]

One possible explanation for chronic pain progression is that it occurs when an afferent stimulation of peripheral nociceptors is retained for a long time due to injuries in deep tissues that do not heal and provoke local pain, generating central sensitization.[32] Potentially, MT can improve CMP by limiting the time that these harmful stimuli are sent to the nervous central system.[32] This is because MT is a desensitizing therapy that changes the pain memory and generates a new and secure memory in the brain.[38]

Usually, studies with low methodological quality are biased to present a better effect favoring manual therapy, in opposition to what was observed in the present systematic review. The quality assessment of the included studies by the PEDro scale showed that the study with the worst quality (score 4)[26] was the study with the highest weight in the meta-analysis (35.8%) (Fig 2). Meanwhile the study with the best methodological quality (score 9)[28] had the smallest weight (8.1%). Nevertheless, the study with the best quality demonstrated a larger mean difference in favor of MT when compared with the study with the lowest quality.[26,28] Thus, the meta-analysis performed in the present study is probably a reliable representation of the effects of MT treatment.

Limitations of the present study include those inherent to all systematic reviews and should be considered when interpreting the results. The first limitation is the lack of details regarding pain characteristics and insufficient information about, for example, musculoskeletal tissue behavior after MT techniques. Other limitations are the small sample size in the included studies, the small number of articles included, and low methodological quality of some of the included studies. Thus, larger sample sizes and carefully planned designs are required for future analysis, as well as better monitoring of selected parameters to provide appropriate future suggestions. These improvements might increase specific understanding of the effectiveness of MT in clinical practice.

Overall, research assessing the potential effects of MT on upper limb and thorax dysfunctions among female breast cancer survivors is still required, to further understand the role of different techniques, methods, and dosage of delivery.

Conclusion

Current evidence shows that MT is effective for treating CMP in the upper limbs and thorax of female breast cancer survivors, by decreasing CMP intensity and increasing the pressure pain threshold.

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Contributorship Information

Concept development (provided idea for the research): F.P.d.S., F.F.S.
Design (planned the methods to generate the results): F.P.d.S., M.A.d.N., F.F.S.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): M.A.d.N., F.F.S.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): F.P.d.S., G.M.M., K.Z.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): F.P.d.S., G.M.M., K.Z.
Literature search (performed the literature search): F.P.d.S.
Writing (responsible for writing a substantive part of the manuscript): F.P.d.S., F.F.S.

Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): M.A.d.N., F.F.S.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmpt.2018.12.007.

Practical Applications

- Manual therapy has been included in the treatment of chronic musculoskeletal pain in women who are surviving breast cancer.
- Manual therapy does not improve the QOL of women surviving breast cancer.
- Manual therapy was considered effective for treating CMP in the upper limbs and thorax of female breast cancer survivors.

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