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Original Research

Manual Lymph Drainage With Progressive Arm Exercises for Axillary Web Syndrome After Breast Cancer Surgery: A Randomized Controlled Trial

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Abstract

Objective. This study aimed to determine the effectiveness of a physical therapist–designed program tailored to axillary web syndrome (AWS) in women after breast cancer surgery.

Methods. A prospective, single-center, assessor-blinded, randomized controlled trial was conducted at the Physiotherapy in Women's Health Research Unit of the Alcalá University (Madrid, Spain). Ninety-six women with AWS were assigned to the physical therapy group (manual lymph drainage [MLD] using resorption strokes and arm exercises as if performing median nerve neurodynamic glide exercises with no neural loading; n = 48) or the control group (standard arm exercises; n = 48), with both groups receiving treatment 3 times a week for 3 weeks. Both interventions included an educational component.

Results. Compared with the control group, the physical therapy group showed significant and clinically relevant improvements in the primary outcome (self-reported pain intensity) at the primary and 3-month follow-ups. Significant and clinically relevant differences between groups were also found in the secondary outcomes (shoulder active range of motion, shoulder disability, and physical and functional aspects of health-related quality of life) at the primary follow-up and in the secondary outcomes as well as the trial outcome index at the 3-month follow-up. No significant differences were found at the 6-month follow-up in either primary or secondary outcomes.

Conclusion. The physical therapy program tailored to AWS was found to be effective for AWS symptoms in women after breast cancer surgery, both immediately after the program and after 3 months.

Impact. To our knowledge, this is the first appropriately designed study to demonstrate the effectiveness of MLD with progressive arm exercises for AWS. Clinicians and health service providers should consider how to provide survivors of breast cancer with AWS the opportunity to participate in physical therapy programs, including MLD with progressive arm exercises.

Lay Summary. For axillary web syndrome following breast cancer surgery, a physical therapist can design a treatment program including manual lymph drainage and progressive arm exercises, which has been shown to result in reduced pain and improved motion compared with standard arm exercises.

Keywords: Arm Volume, Axillary Web Syndrome, Breast Neoplasms, Pain, Physical Therapy Modalities, Quality of Life, Range of Motion, Shoulder Dysfunction

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Introduction

Axillary web syndrome (AWS) is a common complication in women with breast cancer occurring in the early postoperative period (within 8 weeks) after axillary surgery.[1–4] Its incidence can be as high as 85.4% depending on the type of axillary surgery (axillary lymph node dissection or sentinel lymph node dissection), the frequency of follow-up, and the diagnosis criteria.[1,2,4] Although Moskovit et al[3] coined the term axillary web syndrome, it was first described by Ferrandez and Serin[5,6] in 1996 as superficial lymphatic thrombosis. The underlying pathophysiology remains uncertain, although 1 study carried out with biopsies of AWS[7] cords seemed to support the findings of other previous studies[1] as well as the Ferrandez and Serin hypothesis,[5,6] which states that AWS represents lymphatic vessel thrombosis. AWS is characterized by the following: axillary pain that runs down the medial arm reaching the elbow—in some cases, pain in the ulnar side of the forearm, wrist, and hand; limited shoulder range of motion (ROM)—mainly for abduction; and cords of tissue (like guitar strings) extending from the axilla into the medial arm, which are visible or palpable, and painful shoulder abduction. Reduced shoulder ROM and pain by movement may cause distress to the individual and problems with positioning the arm for radiotherapy.[5] AWS remains a poorly understood and under-recognized postoperative complication of breast cancer surgery. Although it is increasingly described in peer-reviewed literature,[2–4,8–13] properly designed and powered studies on effective treatment are lacking.[11,14] Early literature stated that AWS resolves spontaneously within 3 to 4 months of onset[2,3]; however, recent studies provide contrary evidence, with AWS at times persisting for years after surgery.[10,15,16] Resolution may also be followed by a later recurrence.[4,16] Several case reports recommend various approaches such as patient education,[11,17–19] active shoulder exercises,[4,17,19] fascia mobilization techniques,[20] therapeutic massage with passive shoulder movements,[21,22] antiphlebitic administration combined with physical therapy,[22] applying moist heat to the axilla and inner arm combined with arm exercises,[23] and shoulder exercises with cohesive bandaging.[18] To our knowledge, only 1 randomized controlled trial has been conducted in which the effects of 4 weeks of physical therapy combined with manual lymph drainage (MLD) was compared with isolated physical therapy[24] in individuals with breast cancer with AWS. MLD has been shown to improve blood and lymphatic circulation and promote interstitial fluid clearance. Increased interstitial fluid clearance is thought to reduce local levels of inflammatory mediators, which are often associated with pain and edema.[6,25–27] Although physical therapy may improve ROM and pain in AWS, more randomized control trials with high methodological accuracy are needed as well as studies comparing different physical therapy and/or pharmacological approaches.[11]

Therefore, this study aimed to determine the effectiveness of a physical therapy program tailored to AWS in improving pain, ROM, perceived shoulder disability, and health-related quality of life (HRQoL).

Methods

We conducted a single-center, randomized, single-blinded, 2-armed parallel group clinical trial of women with AWS after axillary surgery for breast cancer at the Physiotherapy in Women's Health Research Unit of the Alcalá University (Madrid, Spain).

Participants

Participants were recruited from the specialized breast unit of the Príncipe de Asturias University Hospital by their surgical oncologist between January 2016 and May 2020. The inclusion criteria were as follows: unilateral breast cancer, breast surgery with lymphadenectomy and/or sentinel lymph node biopsy, AWS in the upper limb of the operated side, a subjective pain rating of >30 mm assessed via visual analogue scale (VAS), and no contraindications for physical therapy (infection, fever, metastases). The exclusion criteria were as follows: lymphedema, bilateral breast cancer, systemic disease (metastases), infection, fever, locoregional recurrence, neurological disorders, adhesive capsulitis, consumption of analgesic and anti-inflammatory drugs, acute thrombosis, psychiatric disease, and inability to understand and complete the study questionnaires (cognitive impairment and/or visual deficit for reading) or the information and instructions for treatment. AWS on the chest or ipsilateral thorax not involving the arm was also excluded.

The diagnostic criteria for AWS included the following: pain and restriction of shoulder active ROM (AROM) with associated visible or palpable taut tissue cords in the axilla in maximal shoulder abduction; and verified absence of erythema, warmth, or any other inflammatory sign of superficial thrombophlebitis.[4]

The secondary arm lymphedema exclusion criterion was met when a circumference increase of ≥2 cm at any 2 adjacent points on 1 arm compared with the other arm was observed.[28]

After confirming that all referred participants met all inclusion and exclusion criteria (M.J.Y.S), those who agreed to participate provided their written informed consent prior to entering the study. Prior to the intervention, each participant underwent a baseline assessment (A_0) individually.

Randomization and Blinding

After A_0, participants were randomly assigned to the AWS physical therapy group (AWSPt-G) or the control group (CG). A physical therapist (M.J.Y.S), who did not participate in the assessment or in the intervention, used a computer randomization list at a 1:1 ratio (EPIDAT v.3.1, Xunta, Galicia, Spain) to allocate participants consecutively to each group. Allocation was not revealed until each participant had completed A_0, at which point the treating physical therapists (B.N.B. and V.P.G.) and the participants were informed by M.J.Y.S of their group assignment via phone.

Follow-up

Three follow-up visits were scheduled: after completing the intervention (A_1) and at 3 (A_2) and 6 (A_3) months after A_0. The primary follow-up time point, A_1, was at the post-physical therapy assessment conducted in the 2 days following the last session of the 3-week physical therapy intervention period (ie, A_1 is at 3 weeks after A_0). The follow-up appointments were flexible depending on the availability of the participants, who were notified 1 week before their scheduled appointment to confirm or change the day/time.

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Interventions

Both interventions lasted for 3 weeks, with 3 visits each week at 45 minutes per visit in the AWSPt-G and 30 minutes per visit in the CG. Both interventions included an educational component. Each group had 1 physical therapist (B.N.B. or V.P.G.) who delivered all interventions individually. Both groups received the same educational intervention. The physical therapists had more than 10 years of experience in the management of breast cancer and vascular diseases using lymphatic drainage. B.N.B and V.P.G. were aware of the participants' group allocation.

AWS Physical Therapy Group

The AWS physical therapy program included MLD in the axilla and proximal ipsilateral arm using resorption strokes, as described by Theys et al[29] and Ferrandez et al[26]; specific thumb MLD using resorption strokes on the taut cords to make them gradually more flexible[26]; and progressive action-assisted and active arm exercises. The mean duration of MLD was 20 to 30 minutes. The resorption strokes were always applied from the axilla to the elbow as follows: (1) mainly on the axilla and medial aspect of the arm, progressing from the proximal to the distal third of the arm; (2) specific thumb MLD on the taut cords according to their characteristics and size from the axilla to the forearm; and (3) on the axilla and proximal third of the arm. Arm exercises consisted of stretching the arm in (1) shoulder abduction, extension, and external rotation; (2) elbow extension and forearm supination; and (3) wrist and finger extension as if performing median nerve neurodynamic glide exercises with no loading of neural tissues, with the neck in contralateral side bending[30] (Suppl. Appendix). After each treatment session, the participants were instructed to perform the exercises at home with 1 to 3 sets of 5 to 10 repetitions, 1 to 3 times per day. The instructions emphasized that the exercises must be "painless, without overcoming a comfortable tightness."[19]

CG Protocol

The CG protocol included standard arm exercises that are reportedly effective[28,31–33] for recovering upper limb mobility after breast cancer surgery. The exercises consisted of progressive active shoulder exercises, in conjunction with functional activities and active proprioceptive neuromuscular facilitation exercises, in 2 diagonal symmetrical bilateral patterns and asymmetrical reciprocal patterns.[28] These exercises are considered usual-care practice[28,34,35] and were taught in the first intervention session. The participants were instructed to perform the exercises at home with 1 to 3 sets of 5 to 10 repetitions, 1 to 3 times per day. Considering ethical issues, including a no-intervention CG or a CG with only reassurance that the syndrome will resolve spontaneously as a comparator to the experimental group was not proposed.

In both groups, the arm exercises progressed as pain permitted.

Educational Strategy (Both Groups)

The educational strategy consisted of instruction with printed materials on the side effects of surgery (seroma, AWS, impaired shoulder movement, impaired arm sensitivity, pain); the anatomy, physiology, and physiopathology of the lymphatic and venous systems; concepts of normal load versus overload; causes of AWS and secondary lymphedema; identifying possible precipitating factors; and the 4 categories of interventions to prevent secondary lymphedema (prevention of infection, avoidance of arm constriction, and use and exercise of the arm), together with individual strategies for implementing these measures.[28,36]

Physical Therapy Assessment

A different physical therapist specializing in women's health (M.T.L.), who remained blinded to participant group allocation performed all baseline and follow-up assessments. The participants were instructed not to reveal their allocation to M.T.L. A_0 was conducted on the day the participants agreed to participate in the study, which was 2 days before starting treatment.

At A_0, we collected personal and clinical data including age, body mass index, breast cancer surgery, adjuvant therapies, number of lymph nodes removed, and affected arm (dominant or non-dominant). At A_0 and all other assessments, the following outcomes were collected by M.T.L.:

A) Primary outcome:

(1) Subjective pain intensity, measured using a 100-mm horizontal VAS marked "no pain" on the left and "worst imaginable pain" on the right. The reproducibility and validity of the VAS have been documented in other studies.[37,38] A minimal detectable change (MDC) of 9 to 11 mm is required for clinical relevance.[39]

B) Secondary outcomes:

(2) AROM, for the glenohumeral flexion and abduction, measured according to the methods described by Green et al.[40] AROM was measured in the sitting position, ensuring no trunk movement, using a digital inclinometer (Baseline Digital Inclinometer, Fabrication Enterprises Inc., New York, NY, USA). An MDC of 20.8 degrees for abduction and 10.2 degrees for flexion are required for clinical relevance.[41]

(3) Perceived shoulder disability, assessed using the self-reported Oxford shoulder score (OSS). The OSS is a unidimensional score comprising 12 questions about pain and disability involved in daily activities. Each question is scored from 0 to 4, with 4 representing the best outcome/fewest symptoms. Scores from each question are summed so that the overall score ranges from 0 to 48, with 48 being the best outcome. Lower scores indicate more pain and disability. The OSS Spanish version is applicable, reliable, valid, and responsive for assessing shoulder disability in Spanish women after breast cancer treatment.[42] An MDC of 6 points is required for clinical relevance.[43]

(4) HRQoL, measured using the Functional Assessment of Cancer Therapy-Breast (FACT-B) Spanish version 4. FACT-Bv4 is a 40-item questionnaire designed to measure multidimensional HRQoL in women with breast cancer. The 40 items cover 4 generic scales of well-being (physical, emotional, social, and functional) and 2 side-specific subscales: breast cancer (9 items) and arm (4 items). The arm-specific subscale assesses arm morbidity: (1) pain, (2) poor range of arm movements, (3) numbness, and (4) stiffness. The breast cancer subscale (BCS) and the arm subscale scores range from 0 to 56 points. The

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sum of the BCS and the physical and functional well-being scales is the trial outcome index (TOI; range, 0–92 points). The FACT-B total score ranges from 0 to 144, with a higher score indicating better HRQoL. FACT-B is easy to administer, brief, reliable, valid, and responsive to change.[44] MDCs of 7 points (FACT-Bv4), 2 points (BCS), and 5 points (TOI) are required for clinical relevance.[45]

Arm volume was also measured by M.T.L. at all assessments to detect the onset of lymphedema. A perimeter measurement was used to assess limb volume according to the methods described by Torres-Lacomba et al.[28] Arm perimeters were measured using a standard 1-cm-wide, retractable fiberglass tailor's tape measure (Babel, Madrid, Spain) at 5-cm intervals along both arms, using the elbow fold as the landmark starting point. Volume was calculated by considering each segment as a truncated cone and calculating the segmental volume using the formula described ($V = h \times (C1^2 + C1C2 + C2^2)/12\pi$).[28] Total limb volume between the wrist and the upper boundary was obtained by adding the segmental volumes between these points.[46] The volume of the hand was excluded because it was difficult to model with a truncated cone. Truncated cone calculations of limb segment volumes using circumferential measurement of segments are reportedly reliable.[28] An MDC of 55 mL is required for clinical relevance.[47]

During the intervention, home exercise adherence was monitored using a 1-time diary.

Data Analysis

Power Calculation and Sample Size

The study was designed to detect a between-group difference in pain intensity of 21 mm (SD, 30 mm) on the VAS. This a priori sample size estimation was calculated according to an ad hoc pilot study previously carried out to test the methods and estimate the sample size. The specifications were: power, 90%; level, 0.05; and possible loss to follow-up, up to 10%. Therefore, a total of 96 participants (48 participants per group) were recruited. The sample size was estimated using the statistical program Granmo 7.12 (Institut Municipal d'Investigació Mèdica, Barcelona, Spain, 2012).

Statistical Analysis

Blind statistical analyses were conducted. Participants' characteristics, relevant clinical variables, shoulder disability, and HRQoL were compared between the 2 groups at A_0 using descriptive statistics. Continuous variables were analyzed using Shapiro–Wilk and Levene's tests for testing normal distribution and homogeneity in variance, respectively. For the continuous variables, Student's *t* test was used to examine the between-group differences in sociodemographic and clinical characteristics. For the categorical variables, the χ^2 test was used. The FACT-B scores were calculated according to the FACT-B guidelines, including missing values (which arose when participants did not answer individual questions) that were appropriately considered in the score calculation. This means that the missing values were imputed because the mean of observed items provided more than one-half of the items comprising a subscale.[48]

To estimate the average change from A_0 to subsequent assessments (A_1, A_2, and A_3) and between assessments for each continuous outcome (VAS, AROM, arm volume, perceived shoulder disability, and HRQoL), 4 × 2 mixed analyses of variance were performed with time (baseline, post intervention, 3 and 6 months post intervention) as the within-subjects factor, and group (AWSPt-G, CG) as the between-subjects factor. Post hoc analyses were conducted using Bonferroni correction ($P < .025$).

The results of the between-group comparison are presented as the adjusted mean, CI, and *P* value.

All statistical tests were performed using the statistical package SPSS (IBM SPSS Statistics for Windows, Version 22.0. IBM Corp. Armonk, NY, USA) at a significance level of $\alpha = .05$.

Role of the Funding Source

The funders played no role in the design, conduct, or reporting of this study.

Results

All participants were included on AWS diagnosis, between 2 and 5 weeks after surgery. AWS developed mainly during the 2-week period after surgery, consistent with previously reported findings.[2,4,49] No participant had received radiation therapy or chemotherapy before being diagnosed with AWS. During the follow-up period, 1 participant withdrew from the study due to the onset of secondary lymphedema. Her data were not statistically analyzed at A_3. Finally, 95 participants completed the intervention and follow-up assessments (AWSPt-G, n = 48; CG, n = 47; see CONSORT flow diagram in Fig. 1). The clinical and demographic characteristics at A_0 are shown in Table 1. No significant differences were found between AWSPt and CGs at baseline.

Table 2 shows the mean difference for the primary and secondary outcomes between the 2 groups, from A_0 to each follow-up, together with the 95% CIs and *P* values.

The primary outcome of subjective pain intensity (Tab. 2; Fig. 2) significantly decreased in the AWSPt-G at A_1 ($P < .001$) and A_2 ($P < .001$) compared with the CG. The differences between groups were also clinically meaningful at A_1 (−23.94 mm) and A_2 (−14.22 mm), with a larger effect observed in the AWSPt-G (A_1: −7.94 mm; A_2: −75.22 mm) than in the CG (A_1: −49 mm; A_2: −61 mm).[39] No significant difference was found between groups at A_3 ($P = .08$).

Regarding secondary outcomes, AROM and perceived shoulder disability significantly improved in the AWSPt-G at A_1 and A_3 ($P < .001$) compared with the CG (Tab. 2; Fig. 2). The AWSPt-G also showed clinically meaningful results at A_1 (7.17 points) and at A_2 (6.09 points) for shoulder disability[43] and at A_1 for AROM (flexion = 22.38 degrees; abduction = 38.36 degrees) compared with the CG.[41] No significant differences were found between the 2 groups at A_3 ($P > .05$).

HRQoL improved in both groups at A_1, A_2, and A_3, although the improvement at A_2 was less than those at A_1 and A_3 (Fig. 3; Tab. 2). The BCS and TOI scores significantly improved ($P < .001$) in the AWSPt-G at A_1 and A_2. The BCS scores were also clinically meaningful at A_1 (2.57 points) and A_2 (2.38 points).[45] No significant differences between the 2 groups were found in the BCS and TOI scores at A_3 or in the total FACT-B scores at any follow-up (Fig. 3, Tab. 2; $P > .05$). The level of response in the FACT-B questionnaire during the assessments reached up to 95% of all items completed.

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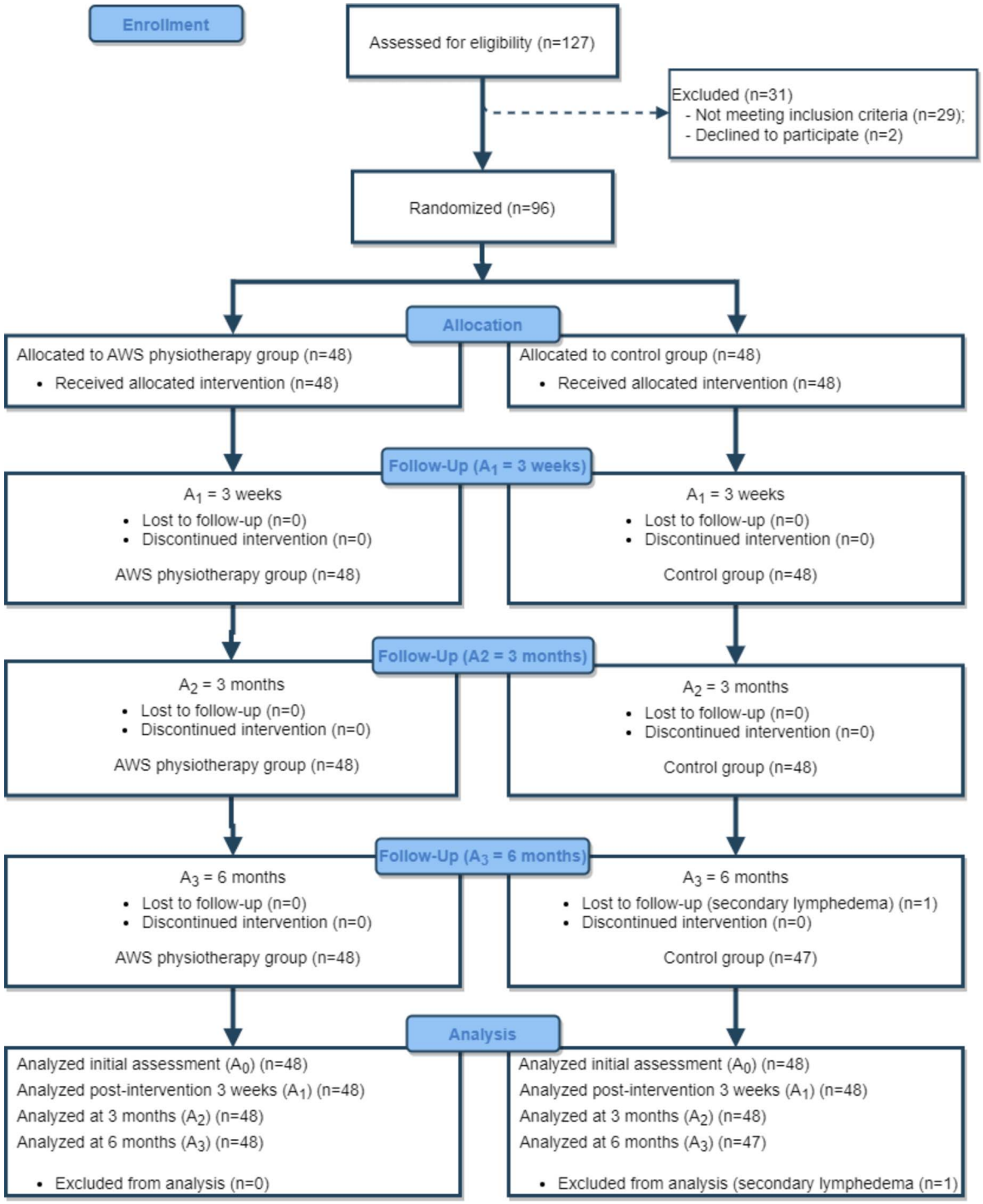

Figure 1. CONSORT flow diagram of participants throughout the study. AWS = axillary web syndrome.

Arm volume improved in both groups throughout the entire follow-up, with the greatest improvement in the AWSPt-G at A_1, A_2, and A_3 (−34.54 mL, −32.90 mL, and − 20.97 mL, respectively, vs the CG).

Adherence rate to the exercise programs during the intervention was similar in both groups, with both groups showing high adherence (AWSPt-G, 92.4%; CG, 89.2%).

No adverse effects were found in any group; however, 3 participants (1 in the AWSPt-G and 2 in the CG) experienced AWS recurrence after adjuvant therapy (chemotherapy and radiotherapy).

Discussion

Our main findings showed that a physical therapy program tailored to AWS with an educational component about reducing AWS symptoms (pain and shoulder AROM) improved participant-perceived shoulder disability and specific physical and functional aspects of HRQoL compared with standard arm exercises with the same educational component. The effects were observed immediately after the program and at the 3-month follow-up. The differences in these changes were clinically meaningful relative to the standard arm exercises.

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Table 1. Comparison Between Randomized Groups at Baseline[a,b]

Characteristics	AWSPt Group (n = 48)	Control Group (n = 48)	Total Sample (n = 96)	*P*
Age, mean (SD), y	48.7 (9.3)	48.3 (10.8)	48.6 (11.2)	.846
BMI, mean (SD), kg/m^2	25.2 (4.9)	24.8 (4.2)	25.1 (4.8)	.449
Education level				.683
Primary school	10 (20.8)	9 (18.8)	19 (19.8)	
High school	15 (32.2)	15 (32.2)	30 (31.2)	
College or university	23 (47.9)	24 (50)	47 (49)	
In employment	32 (66.6)	34 (70.8)	66 (68.7)	
Similar dominance and breast surgery side	36 (75)	35 (72.9)	71 (74)	.998
Surgical procedure				.583
Modified mastectomy	11 (22.9)	13 (27.1)	24 (25)	
Quadrantectomy	17 (35.4)	16 (33.3)	33 (34.4)	
Lumpectomy	20 (41.7)	19 (39.6)	39 (40.6)	
Axillary dissection procedure				.997
ALND	36 (75)	35 (72.9)	71 (73.9)	
SLNB	12 (25)	13 (27.1)	25 (26.1)	
Removed lymph nodes, mean (SD)	10.9 (3.9)	10.6 (4.7)	10.7 (4.3)	.734
Postoperative therapy				
Radiotherapy	40 (83.3)	38 (83)	79 (83.1)	.793
Chemotherapy	34 (70.8)	32 (70.2)	66 (69.5)	.825
Hormonal therapy	26 (60)	27 (60)	53 (55.8)	.999
Time of onset of AWS postsurgery days, median (IQR)	18 (12)	17 (13)	17.5 (12.5)	.696
VAS, mean (SD), mm	74 (4.3)	74.2 (4.7)	74.1 (4.5)	.326
Glenohumeral AROM, mean (SD), °				
Flexion	118.2 (9)	121.3 (8.8)	119.9 (8.9)	.899
Abduction	95.3 (14.7)	93.9 (16.2)	94.6 (15.5)	.563
Arm volume affected region, mean (SD), mL	1495.3 (239.3)	1499.4 (204.5)	1497.4 (221.9)	.344
OSS	24.6 (3.1)	25.2 (2.5)	24.9 (2.8)	.782
BCS, mean (SD)	28.2 (2.9)	29.1 (1.2)	28.7 (2)	.212
FACT-B, mean (SD)	107.7 (5)	106.2 (5.2)	106.9 (5.1)	.571
TOI, mean (SD)	65.9 (3.6)	66.1 (4.1)	66 (3.8)	.490

[a] AWSPt = axillary web syndrome physical therapy group; BCS = Breast Cancer Subscale of Functional Assessment of Cancer Therapy-Breast Questionnaire; BMI = body mass index; FACT-B = total score of Functional Assessment of Cancer Therapy-Breast Questionnaire; OSS = Oxford Shoulder Score Questionnaire; TOI = Trial Outcome Index of Functional Assessment of Cancer Therapy-Breast Questionnaire; VAS = visual analogue scale. [b] Values are numbers (percentages) unless stated otherwise.

This indicates that the changes achieved with the physiotherapy intervention were significant for the participants. These results are likely attributable to the inclusion of different techniques designed to specifically address pain and lack of extensibility in lymphatic vessels. AWS is associated with superficial lymphatic thrombosis in relation to local lymph stasis caused by axillary lymph node dissection. Two studies that examined AWS cord biopsies with D2–40 (lymphatic endothelial cell) staining excluded venous pathology, suggesting a lymphatic origin.[7,50] Superficial lymphatic thrombosis is accompanied by local stasis, hypercoagulation, inflammation triggering pain, and lack of extensibility of the involved superficial lymphatic vessels. This lack of extensibility gives lymphatic vessels a cording appearance. AWS follows the course of the upper arm and forearm lymphatic vessels, reaching the base of the thumb,[4,51] which explains its location and the pain experienced during stretching (shoulder abduction and external rotation, elbow extension, forearm supination, and wrist and finger extension). Shoulder movements increase tension in the cords, thereby increasing pain and limiting the AROM.[9] In the AWSPt-G, progressive upper limb exercises were focused on the movements that stretch the taut cords, which explains the improved results regarding pain, AROM, and perceived shoulder disability. MLD was also applied to the axilla, on the arm, and following the taut cords[26] to gradually increase their flexibility; this may have helped the flexibility of the vessels and the recanalization of the thrombus, eventually restoring lymphatic flow. MLD improves lymphatic circulation and edema resorption and is effective for lymphedema because it improves the removal of fluid from interstitial spaces.[25]

Women with breast cancer undergoing treatment often experience many psychological and physical adverse effects that impair their HRQoL. Breast cancer symptoms, such as pain, fatigue, arm morbidity, and postmenopausal symptoms, are among the most common symptoms reported by breast cancer survivors and are directly associated with a decreased HRQoL.[52] In our study, the FACT-B scale used to assess HRQoL showed relatively low scores at A_0, consistent with previous reports evaluating HRQoL in women treated for breast cancer, especially after surgery.[53] Our results for the BCS scores indicated clinically meaningful changes for the AWSPt-G compared with the CG immediately after the intervention and at 3 months follow-up. This further supports the superiority of the physical therapy intervention. However, despite the statistically significant changes for the TOI between the 2 groups, these changes were not clinically relevant. The TOI subscale, which is the sum of physical well-being, functional well-being, and BCS scores, is an efficient summary of the physical and functional aspects of HRQoL. Pain and limited AROM are known to adversely influence functional capacity and the HRQoL.[54] The improved results for pain, shoulder AROM, and perceived shoulder disability in the AWSPt-G compared with the CG could explain the improvements in the physical and functional aspects of

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Table 2. Difference in Means for Each Outcome Between Groups (AWSPt Group vs Control Group) at Different Time Points[a]

Outcome	A	Mean Difference (95% CI)[b]	*P*
VAS (mm)	A_0	−1.04 (−2.91 to 0.82)	.269
VAS (mm)	A_1	**−23.94** (−25.78 to −22.10)[c]	<.001[c]
VAS (mm)	A_2	**−14.22** (−15.53 to −12.90)[c]	<.001[c]
VAS (mm)	A_3	−0.36 (−0.78 to −0.49)	.083[d]
Flexion AROM (°)	A_0	−2.98 (−6.62 to 0.66)	.107
Flexion AROM (°)	A_1	**22.38** (19.16 to 25.61)[c]	<.00[c]
Flexion AROM (°)	A_2	6.04 (4.49 to 7.59)[c]	<.001[c]
Flexion AROM (°)	A_3	0.16 (−0.80 to 1.12)	.738[d]
Abduction AROM (°)	A_0	1.48 (−4.88 to 7.85)	.645
Abduction AROM (°)	A_1	**38.36** (31.91 to 44.81)[c]	<.001[c]
Abduction AROM (°)	A_2	9.80 (7.71 to 11.89)[c]	<.01[c]
Abduction AROM (°)	A_3	0.89 (0.65 to 1.83)	.676[c]
OSS	A_0	−0.59 (−1.70 to 0.52)	.294
OSS	A_1	**7.17** (6.39 to 7.95)[c]	<.001[c]
OSS	A_2	**6.09** (5.51 to 6.68)[c]	<.001[c]
OSS	A_3	0.17 (0.34; 0.85)	.509[d]
BCS	A_0	−0.81 (−1.74 to 0.12)	.087
BCS	A_1	**2.57** (1.70 to 3.45)[c]	<.001[c]
BCS	A_2	**2.38** (1.41 to 3.35)[c]	<.001[c]
BCS	A_3	0.93 (0.08 to 1.18)	.055[d]
FACT-B	A_0	1.52 (−0.58 to 3.61)	.154
FACT-B	A_1	1.73 (−0.06 to 3.51)	.058
FACT-B	A_2	0.82 (−1.56 to 3.19)	.495
FACT-B	A_3	1.05 (−0.19 to 2.29)	.096
TOI	A_0	−0.32 (−1.90 to 1.26)	.691
TOI	A_1	3.23 (2.08 to 4.39)[c]	<.001[c]
TOI	A_2	3.06 (2.19 to 3.92)[c]	<.001[c]
TOI	A_3	0.47 (−1.48 to 0.53)	.354[d]

[a] A = assessment; A_0 = baseline assessment; A_1 = postintervention (3 wk) assessment; A_2 = 3-month follow-up postintervention assessment; A_3 = 6-month follow-up postintervention assessment; AROM = active range of motion; AWSPt = axillary web syndrome physical therapy; BCS = Breast Cancer Subscale of Functional Assessment of Cancer Therapy-Breast Questionnaire; FACT-B = total score of Functional Assessment of Cancer Therapy-Breast Questionnaire; OSS = Oxford Shoulder Score Questionnaire; TOI = Trial Outcome Index of Functional Assessment of Cancer Therapy-Breast Questionnaire; VAS = visual analogue scale. [b] The mean difference between groups that showed minimal detectable change is highlighted in bold. [c] The mean difference and CI that showed significant differences between groups. [d] Excluded 1 participant lost to follow-up in control group.

HRQoL. Exercise adherence is essential to maintain HRQoL. The participants in this study showed high adherence to their exercise programs during the intervention. This may be due to the attention and monitoring provided by the researchers and fewer exercise limitations due to cancer treatment, which are among the most prominent predictors of adherence to exercise interventions.[55] FACT-B total scores were also higher in the AWSPt-G than in the CG, but the difference was not statistically significant. Consistent with our results, several studies stated that global HRQoL was minimally or not impaired in cancer patients compared with the general population, despite the specific functioning and symptom subscales showing significant disability.[52,56]

No statistically significant differences were found between the groups at A_3 in any variable. This finding could be linked to a spontaneous improvement in the CG, consistent with early studies that state that AWS resolves spontaneously within 3 to 4 months of onset.[2,3]

Chronic pain is one of the most frequent long-term complications of cancer. Approximately 30% of breast cancer survivors are confronted with above-average pain 10 years after finishing treatment.[57] The most important clinical risk factors for developing chronic pain are pain intensity and pain frequency. The greater the intensity, number of sites, and duration, the more likely chronic pain is to develop.[58] Prolonged nociceptor activation can increase pain perception and sensitization and predispose a patient to develop chronic pain.[59] Axillary lymph node dissection and chemotherapy or radiotherapy, among other factors, have been associated with the risk of developing persistent pain in breast cancer survivors.[57] Furthermore, having more than 1 cause of chronic pain and pain of longer duration are both associated with poorer quality of life.[58,60] In this sense, the present study shows that a physical therapy program tailored to AWS significantly reduced pain immediately after the 3-week therapy period and before the start of adjuvant chemotherapy and radiotherapy treatments, shortening the recovery time by at least 3 months. One of the most important ways to reduce chronic pain incidence is to prevent acute pain from occurring and managing it well when it does occur.[58]

Comparison With Other Studies

Although several case reports have provided results on AWS treatment, there is no apparent consensus on the optimal approach.[4,11,17–23] To our best knowledge, only 1 randomized clinical trial has examined the effect of MLD on shoulder function, pain, lymphedema, and HRQoL in breast cancer patients with AWS.[24] Cho et al[24] compared isolated physical therapy versus physical therapy plus MLD in 48 women with breast cancer (n = 24 per group). All recruited women presented with palpable or visible cords on the arm and had pain in the arm for at least 4 weeks after surgery. Both groups received the same arm exercise program 3 times weekly for 4 weeks, which consisted of stretching and strengthening exercises for the upper limb, tissue mobilization,

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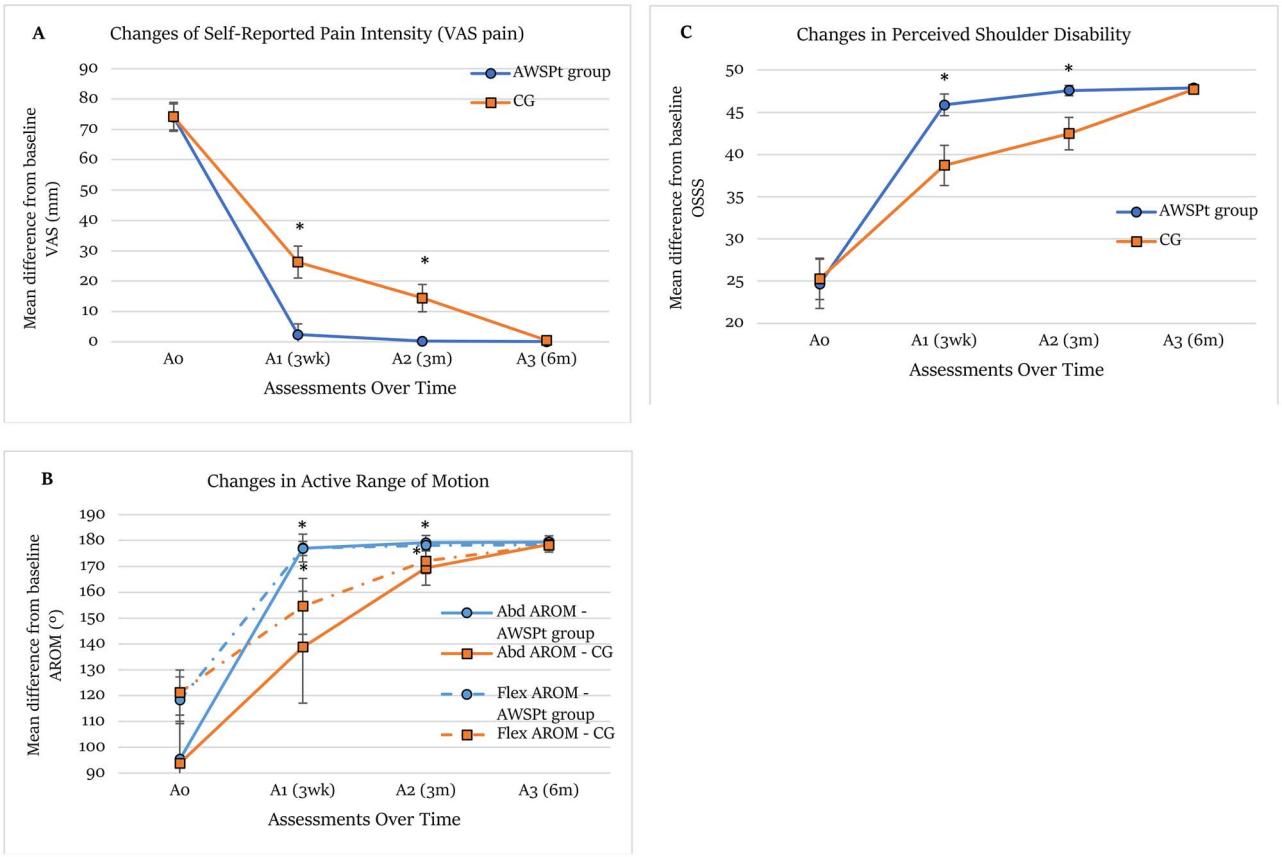

Figure 2. Changes in pain, active range of motion (AROM), and perceived shoulder disability over time in both groups (mean [SD]). (A) Changes in subjective pain intensity throughout this study in the 2 groups showing the effects in each group. (B) Changes in the AROM throughout this study in the 2 groups showing the effects in each group. (C) Changes in perceived shoulder disability throughout this study in the 2 groups showing the effects in each group at post intervention (3 weeks), and 3- and 6-month follow-up post intervention. *$P < .001$. A = assessment; AWSPt-group = Axillary Web Syndrome Physical Therapy group; CG = control group; OSS = Oxford Shoulder Score Questionnaire; VAS = visual analogue scale.

scapular mobilization, shoulder ROM exercises, and stretching of the tight cords in shoulder abduction. In addition, 1 group received 30 minutes of MLD using the Vodder method, 5 times daily for 1 week, with instructions to perform the method at home for the other 2 to 4 weeks of the program. Both groups showed significant improvements in HRQoL, shoulder flexion strength, arm function, and pain, with significantly greater improvements in pain and arm volume reductions for the physical therapy plus MLD group. Although these results seem to support those of our study regarding the effects immediately after the intervention, differences in research design and methodology led us to compare them cautiously. In the study by Cho et al,[24] there was no control or follow-up and no information on exercise adherence or whether the participants were instructed to perform the exercises at home, nor did they offer enough detail on arm exercises more focused on the taut cords. Regarding MLD, they did not provide enough details about the areas to which it was applied; the Vodder method was cited, which suggests that the application was extended to areas without taut cords. In addition, MLD was applied only to the axilla, without following the taut cords along the arm.

Strengths and Limitations

We believe our study provides evidence that a physical therapy program tailored to AWS has positive effects on its AWS impairments after the program and at 3 months follow-up. However, this study is limited in that it was a single-center study. Although we have no reason to suspect systematic differences in care provided by this hospital and other hospitals (regional or in other developed countries), this may limit the external validity of the results. In addition, although the measurements were blinded to the participants' treatment allocation and both groups were reasonably balanced for baseline characteristics, the physical therapists who delivered the program were trained in the treatment of breast cancer patients, which may have strengthened the study but also limited the generalizability of this intervention to other settings. However, the clinical relevance of the results, as well as the study design, might support a multicenter study.

Future Research Directions

Our results, as well as those reported by Cho et al,[24] showed a shortening of the natural course of AWS, with symptoms reduced in 9 and 12 treatment sessions, respectively. Future studies should aim to clarify the physical therapy dosage and frequency that allow faster recovery from AWS. In addition, further research should also include randomized controlled trials comparing physical therapy with analgesic or anti-inflammatory drugs and their combination, along with a cost-effectiveness analysis.

Some studies proposed that patients with AWS have a higher risk of developing lymphedema.[4,12,15,28,61] This link between AWS and secondary lymphedema could be explained

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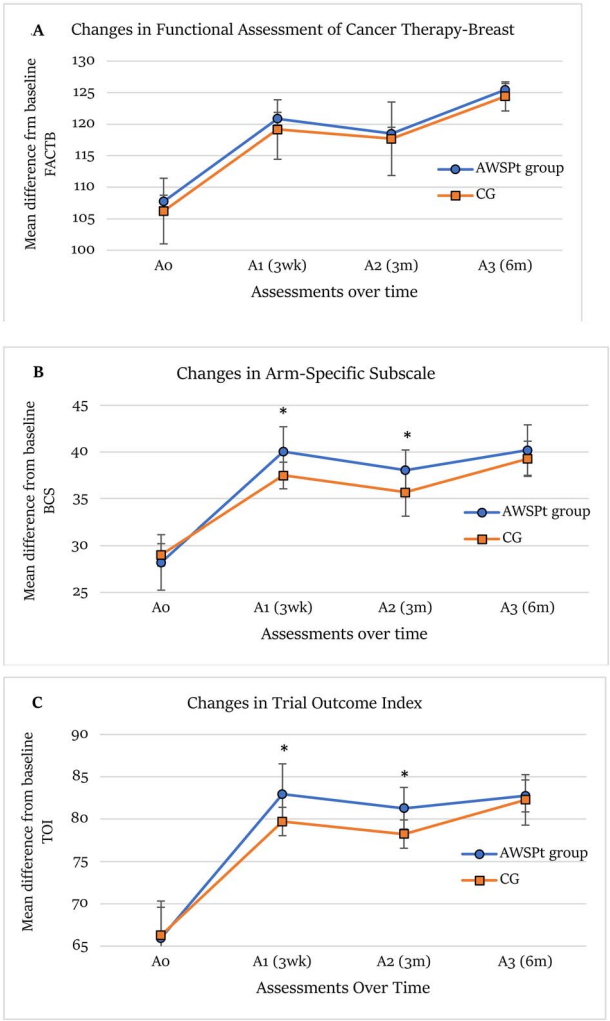

Figure 3. Changes in health-related quality of life over time in both groups [mean (SD)]. Changes in (A) Functional Assessment of Cancer Therapy-Breast throughout this study in the 2 groups; (B) arm-specific subscale throughout this study in the 2 groups; and (C) the Trial Outcome Index throughout this study in the 2 groups showing the effects in each group at post-intervention (3 weeks) and 3- and 6-month follow-up post intervention. *$P < .001$. A = assessment; AWSPt-group = axillary web syndrome physical therapy group; BCS = Breast Cancer Subscale of Functional Assessment of Cancer Therapy-Breast Questionnaire; CG = control group; FACT-B = Total score of Functional Assessment of Cancer Therapy-Breast Questionnaire; HRQoL = health-related quality of life; TOI = Trial Outcome Index of Functional Assessment of Cancer Therapy-Breast Questionnaire.

by AWS being a sign of injury to the lymphatic system, which potentially produces a lymphatic overload. This overload, together with other factors (eg, radiotherapy[62] and chemotherapy[63]), could be responsible for secondary lymphedema onset. Further research is needed to determine the scope and severity of complications associated with AWS, especially with regards to its possible association with subsequent lymphedema.

AWS is an early complication of axillary surgery for breast cancer (either axillary lymph node dissection or sentinel lymph node biopsy), which is more common than infection, seroma, or lymphedema.[64] It is also a source of nociceptive pain, which can have an important impact on the HRQoL of breast cancer patients. Beacuse this condition can also recur and appear in the medium- and long-term period after surgery, close collaboration of surgeons, radiation oncologists, medical oncologists, primary care providers, and physical therapists is essential for the prevention and management of AWS.

A physical therapy program tailored to AWS was delivered to women with AWS after breast cancer surgery. The program consisted of MLD in the arm and on the taut cords, in conjunction with progressive active and action-assisted arm exercises focused on stretching taut cords. Immediately after the 3-week program and at the 3-month follow-up, the participants who underwent the program experienced significantly reduced pain, enhanced shoulder function and disability, and improved specific functional and physical aspects of HRQoL. These results emphasize the role of physical therapy in the awareness, early diagnosis, and treatment of AWS.

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Providing facilities/equipment: M. Torres-Lacomba, M.J. Yuste-Sánchez
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All authors have read and agreed to the published version of the manuscript.

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Ethics Approval

This research was approved by the Clinical Research Committee of the Principe de Asturias Hospital (OE32/2014). Written and informed participant consent was obtained, and CONSORT guidelines were followed.

Clinical Trial Registration

The study was registered at ClinicalTrials.gov (NCT02224261).

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Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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