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Effect of Bee Venom phonophoresis on shoulder dysfunction post-mastectomy

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***Abstract*---**Background: Breast cancer survivors frequently experience shoulder pain and decreased range of motion, making their daily activities more difficult. No previous studies have established the results of bee venom phonophoresis in the treatment of shoulder dysfunction post-mastectomy. Therefore, this work aimed to evaluate if bee venom phonophoresis has beneficial effects on improving the shoulder pain, dysfunction, and range of motion in post-mastectomy patients. Methods: This randomized controlled trial was carried out between November 2021 and April 2022. Forty female patients aging from 40-to 65 years suffering from shoulder dysfunction 3 to 6 months following modified radical mastectomy were randomly divided into two equal-sized groups: a study group (Group A) who received bee venom phonophoresis with pulsed ultrasound around the shoulder and a control group (Group B) who received pulsed ultrasound around the shoulder only. Three consecutive weeks of three sessions per week were devoted to the intervention program. Patients in both groups received their medical care and selected exercise program (shoulder circles figure, arm lifts figure, wand exercise figure, wall climbing& corner wall stretch). The shoulder pain and disability index (SPADI) and getmyROM mobile application were used to assess the patients

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before and after the interventions. Results: Patients with NS-CLBP (N=90) were randomly assigned to three groups: group A (stabilization + traditional therapy), group B (Pilates plus traditional therapy), and group C (traditional therapy) for 12 sessions over six weeks. Outcome measures: A Walkway pressure measurement system, The Visual Analog Scale, Modified Oswestry Disability Questionnaire, Biering–Sorensen test, and trunk flexion endurance test were adopted successfully to assess both spatial and temporal parameters, pain, function, and isometric endurance of trunk extensor and flexor sequentially. Results: At the baseline evaluation, no significant variations in age were seen between the two groups, SPADI ($p = 0.42$) and shoulder abduction & flexion ROM ($p > 0.05$). While the post-intervention measures revealed that there was a significant decrease in SPADI post-treatment in groups A and B ($p > 0.001$) and a significant increase in shoulder abduction and flexion ROM post-treatment in groups A and B when compared with the pre-treatment measures ($p > 0.001$). Comparison between the post-treatment measures of the two groups revealed non-significant differences in SPADI, shoulder abduction, and flexion ROM ($p > 0.05$). Conclusion: Depending on the study, it can be concluded that bee venom phonophoresis is as effective as traditional ultrasound in improving shoulder dysfunction post-mastectomy.

***Keywords*---**bee venom, shoulder dysfunction, pain, phonophoresis, post-mastectomy.

Introduction

One of the most popular surgical treatments for breast cancer is modified radical mastectomy, which aims to remove the tumor and surrounding tissues [(1)]. Shoulder pain is one of the most common musculoskeletal complaints in post-mastectomy patients. Due to the fibrosis of connective tissue in the shoulder joint, they are susceptible to shoulder pain. Reduced shoulder joint mobility following mastectomy causes connective tissue fibrosis. Shoulder discomfort in post-mastectomy patients is an expensive burden for healthcare providers due to its high prevalence, chronic characteristics, and extensive therapeutic options. It is associated with a diminished sense of well-being and limits activity [(2)]. Shoulder pain and impairment in mastectomy patients can be reduced, although most cases go unreported due to a lack of understanding. Following mastectomy, these women experience a variety of functional and emotional deficiencies, including depression, which have serious psychosocial repercussions [(3)(4)].

Bee venom (BV) is used to treat a range of pain conditions, including neck pain, low back pain, herniated lumbar pain, disc pain, shoulder pain after a stroke, acute ankle sprain, wrist sprain, rheumatoid arthritis, and osteoarthritis of the knee [(5)]. After experimenting with several techniques of bee venom administration, ultrasonic waves (phonophoresis) proved to be the most effective [(6)]. Transdermal drug delivery (TDD) has several advantages over oral drug delivery, including pain

relief and long-term drug release. Phonophoresis is a technique that temporarily improves skin permeability to allow noninvasive delivery of different drugs [7].

Material and Methods

Patients

Between November 2021 and May 2022, a three-week randomized controlled experiment was conducted. Patients were sourced from Egypt's National Cancer Institute in Cairo. Patients signed consent forms stating their interest in participating in the study. The proposal for this study was authorized by the Ethical Committee of Cairo University's Faculty of Physical Therapy in Giza, Egypt (P.T.REC/012/003469). Fifty female patients were recruited and scanned for research eligibility; forty patients who satisfied the inclusion requirements took part in the trial. Ten were excluded (Three participants did not meet the inclusion criteria, while seven declined participation) as shown in Figure (1).

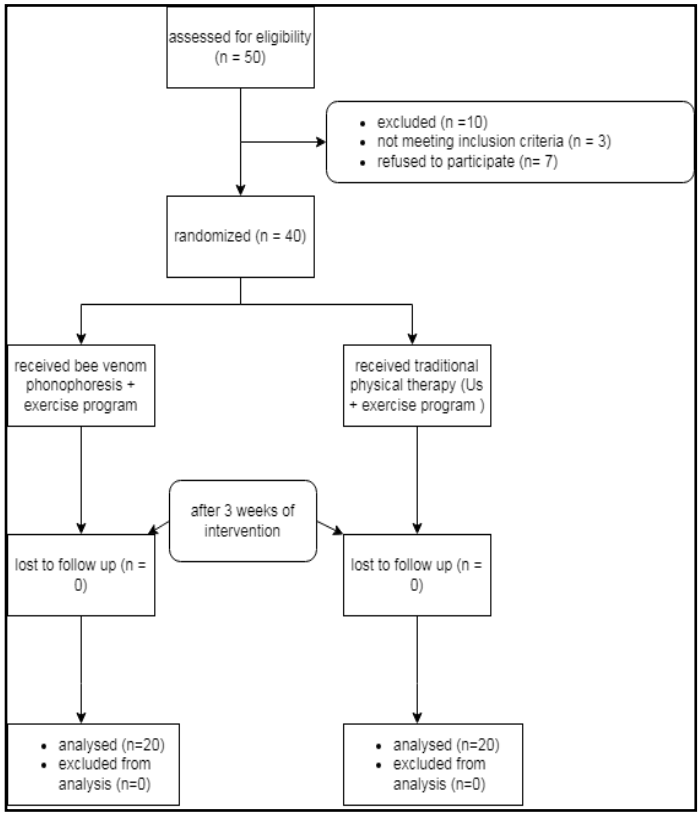

Figure 1. Flow chart of study participants

Females aged 40 to 65 with shoulder dysfunction 3 to 6 months after a modified radical mastectomy were included in the study. Patients with bee venom allergies, mental or psychological disorders, any systemic diseases that might interfere with the study's objectives, vascular problems other than grade 1 lymphedema,

musculoskeletal complications that exacerbate the pain sensation, and those that refused to participate were dropped from the study.

Sample size estimation
Randomization

Block randomization was utilized to ensure that each group had an equal number of eligible patients. Bee venom phonophoresis with pulsed ultrasound around the shoulder was given to Group A, while Group B received only pulsed ultrasound. The same physical therapy exercise program was given to both groups (shoulder circles figure, arm lifts figure, wand exercise figure, wall climbing & corner wall stretch).

Outcome measures

The (SPAD) is a reliable self-administered questionnaire including subscales for pain and disability. The means of the two subscales are added to get a total score on visual analogue scales ranging from 0 (best) to 100 (worst) [8]. Compared to the gold standard comparison (digital inclinometer), the GetmyROM mobile application is a valid and dependable method for capturing precise measurements in clinical settings. It was adapted from the Apple Store to determine shoulder abduction and flexion range of motion [9]. All measures were taken before and after the intervention for three weeks.

Intervention

Both groups of patients received standard medical care and a customized exercise regimen (shoulder circles figure, arm lifts figure, wand exercise figure, wall climbing& corner wall stretch). Group A patients received bee venom phonophoresis with pulsed ultrasound (applicator 1.9 cm2) over the shoulder at a duty cycle of 40% (4 ms on, 6 ms off) and a power density of 0.5 W/cm2. Each session lasted ten minutes, and there were three per week for three weeks (10). Group B received ten minutes of pulsed ultrasound over the shoulder (applicator 1.9 cm2) with a duty cycle of 40% (4 ms on, 6 ms off) and a power density of 0.5 W/cm2 three times per week for three weeks [10].

Statistical procedures

The unpaired t-test was used to compare the mean ages of the two groups. The Chi-squared test was used to compare the distribution of affected limbs across groups. Using the Shapiro-Wilk test, the normality of data distribution was examined. Levene's test for homogeneity of variances was used to examine the homogeneity of variances between groups. The unpaired t-test compared groups' SPADI, shoulder abduction, and shoulder flexion. A paired t-test was conducted to compare pre-and post-treatment results. P> 0.05 was used as the significance criterion for all statistical tests. All statistical analyses were conducted using version 25 of the social studies (SPSS) software for Windows.

Results

Patients' characteristics

Table 1 displays the baseline statistics for both groups. There was no statistically significant difference in mean age or affected sides between the two groups (p <0.05).

Table 1
Basic characteristics of participants

	Group A	Group B	p-value
	Mean± SD	Mean± SD	
Age (years)	50.75 ± 7.35	51.2 ± 6.68	0.84
Affected side (%)			
Right side	11 (55%)	13 (65%)	0.52
Left side	9 (45%)	7 (35%)	

SD, Standard deviation; p-value, the Probability value

Effect of treatment on SPADI, shoulder abduction, and flexion ROM

- **Within-group comparison**
  Groups A and B demonstrated a statistically significant reduction in SPADI post-treatment compared to pre-treatment ($p < 0.001$). Group A has a 64 percent decrease in SPADI, whereas group B has a 59.81 percent decline.
  Groups A and B demonstrated a substantial increase in shoulder abduction and flexion ROM post-treatment compared to pre-treatment ($p > 0.001$). The increase in shoulder abduction and flexion ROM was 64.21 and 74.94 % in group A and 62.07 and 74.07 percent in group B, respectively. (Table 2.)
- **Between groups comparison**
  Before treatment, there were no statistically significant differences between groups ($p > 0.05$). SPADI, shoulder abduction, and flexion ROM were not significantly different between Group A and Group B after treatment ($p > 0.05$) (Table 2).

Table 2
Mean SPADI, shoulder abduction, and flexion ROM pre and post-treatment of groups A and B

	Group A mean ± SD	Group B mean ± SD	MD	p-value
SPADI				
Pre-treatment	85.8 ± 6.89	83.85 ± 8.18	1.95	*P= 0.42*
Post-treatment	30.9 ± 5.46	33.7 ± 6.51	-2.8	*P= 0.151*
MD	54.9	50.15		
p-value	p = 0.001	p = 0.001		

Abduction ROM (degrees)				
Pre-treatment	61.75 ± 3.55	60.5 ± 4.71	1.25	*P= 0.35*
Post-treatment	101.4 ± 6.18	98.05 ± 7.65	3.35	*P= 0.13*
MD	-39.65	-37.55		
p-value	p = 0.001	p = 0.001		
Flexion ROM (degrees)				
Pre-treatment	43.5 ± 4.01	43 ± 3.77	0.5	*P= 0.68*
Post-treatment	76.1 ± 5.01	74.85 ± 4.14	1.25	*P= 0.39*
MD	-32.6	-31.85		
p-value	p = 0.001	p = 0.001		

SD, Standard deviation; p-value, the Probability value

Discussion

This study found that bee venom phonophoresis reduces pain and impairment in patients with shoulder dysfunction after mastectomy while also increasing shoulder abduction and flexion ranges of motion. Its success is due to bee venom phonophoresis's anesthetic and anti-inflammatory effects. The major components of BV include enzymes, peptides, and chemical compounds with low molecular weight (non-peptide substances). Melittin, apamin, and adolapin are the three major peptides in BV [(11)]. When given in large quantities, Melittin causes local pain, itching, and inflammation. Low dosages of this BV molecule, on the other hand, can have a broad anti-inflammatory impact. Interleukin-6 (IL-6), IL-8, tumor necrosis factor (TNF), and interferon (IFN) are inflammatory cytokines that it inhibits. In human keratinocytes treated with porphyromonas gingivalis lipopolysaccharide (PgLPS), melittin inhibits signaling pathways that activate inflammatory cytokines, such as nuclear factor-kappa B (NF-B), protein kinase Akt, and extracellular signal-regulated kinases (ERK1/2). These findings imply that melittin inhibits the basic signaling pathways of inflammatory cytokines, hence reducing inflammation in skin, liver, joint, and brain tissue [(12)].

Furthermore, phonophoresis improves BV penetration into the skin during and after cavitation therapy, causing distorted structured lipids in the stratum corneum. This confusion in the epidermis promotes skin permeability, allowing topical BV to permeate the dermis, especially at a low molecular weight. The topical BV can slowly diffuse through the tissue layers due to a concentration gradient with high concentrations at the skin surface and deeper levels [(13)]. This research supports Jang and Kim (2020) findings that Utilized an ultrasonic device for BV delivery in the treatment of biceps brachii muscle soreness since phonophoresis is a useful method for reducing pain and increasing range of motion. The fact that BV inhibits COX-2 and prostaglandin E2 in the body suggests lower inflammation in various joints. In particular, treatment outcomes have been found in patients with hip osteoarthritis, demonstrating that it improves hip joint mobility. BVA is an injection of BV directly into the skin, whereas BV gel phonophoresis and BV ointment are indirect administration methods. However, ultrasonography aids transdermal medication distribution during phonophoresis [(14)].

Following indirect unilateral inguinal hernioplasty, Rizk et al. (2020) The use of bee venom phonophoresis resulted in a considerable decrease in the visual

analogue scale VAS and an increase in hip range of motion, according to a study (ROM) [10]. In addition, sixty patients were incorporated in the subsequent study conducted by Park et al. (2014). The latter investigated the long-term efficacy of BV acupuncture and physiotherapy in treating adhesive capsulitis. Twenty patients were treated with BV 1 (1:10,000 concentration BVA plus physiotherapy), twenty-two patients were treated with BV 2 (1:30,000 concentration BVA plus physiotherapy), and eighteen patients were not treated (normal saline injection plus physiotherapy). The primary outcome measure was the (SPADI) score. The verbal rating scale for pain and patient satisfaction was used as a secondary outcome measure. The groups' initial characteristics did not differ much. The BV 1 and control groups had significantly different SPADI scores (p=0.043). There were no significant differences in pain verbal rating scores after one year. Additionally, treatment satisfaction was examined, and the BV 1 and BV 2 groups were much more satisfied with their treatment than the control group. A year after treatment, they discovered that BVA and PT together are a powerful combination that is clinically successful and may help patients with AC of the shoulder improve their long-term quality of life [15].

Despite the improvement in this study group, it was determined that there is no meaningful difference between it and the control group. When combined with a specific workout program, the ultrasound led to nearly identical gains in SPADI and shoulder ROM, which may be attributable to the administration of US at a suitable intensity and frequency; it elevates the temperature of high-protein-density soft tissues. The physiological effects of ultrasound include increased blood flow, vascular permeability, local metabolism, improved fibrous tissue extensibility, and muscular relaxation [16]. Stratford et al. found no statistically significant difference between phonophoresis and ultrasound alone to treat pain and dysfunction in patients with lateral epicondylitis [17]. All of the parameters studied by Ay et al. (2010) found no statistically significant improvement in cervical flexion-extension joint mobility, pain levels, trigger point count, NPDI score, or pressure pain threshold ($P > 0.05$). They also found no statistically significant differences between groups 1 and 2 ($P = 0.05$). In patients with MPS, both diclofenac phonophoresis and ultrasound therapy were beneficial. It was discovered that ultrasound therapy is preferable to phonophoresis [18].

This research demonstrates certain advantages. As a starting point, this is the first study to explore the short-term effects of bee venom phonophoresis on post-mastectomy shoulder dysfunction. While bee venom phonophoresis is an efficient and safe method for relieving shoulder discomfort and increasing range of motion in patients who have undergone breast cancer surgery, this study shows that both bee venom plus a regular exercise regimen can have the same impact. The current study has limitations, including limited sample size and no follow-up for both groups. To determine the long-term efficacy of bee venom phonophoresis on shoulder dysfunction following mastectomy, more research with a larger sample size and more observation time is required.

Conclusion

It is concluded that the bee venom phonophoresis combined with exercise is as effective as Us combined with exercise in improving shoulder dysfunction post-

mastectomy. More research with a bigger sample size, longer treatment duration, and long-term observation of different causes of shoulder dysfunction is recommended.

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