STUDY PROTOCOL PLAN AND STADISTICAL ANALYSIS PLAN (SAP)

UNIVERSITY CEU CARDENAL HERRERA

Principal investigator: Dra. Cristina Orts Ruiz

TITLE: Effectiveness of radiofrequency and exercise-based rehabilitation on symptoms associated with pelvic floor dysfunction in breast cancer patients.

Research and Ethics Committee of CEU Cardenal Herrera University Number: CEEI24/540

NCT ID:

DATE: 11-14-2024

STUDY PROTOCOL PLAN

Objectives:

The objectives of our study have been the following:

The aim of the study is to compare the effectiveness of radiofrecuency (RF)-based treatment with pelvic floor muscle treatment (PFMT)-based treatment on genitourinary menopausal syndrome (GUS)-related pelvic dysfunction in breast cancer patients.

Specific objectives

To evaluate the effect of RF, PFMT and the combination of both therapies on urinary incontinence (UI), fecal incontinence (FI) and prolapse in women diagnosed with breast cancer.

To evaluate the effect of RF therapy and PFMT on the quality of life of women diagnosed with breast cancer.

To analyse the effect of RF and PFMT on sexual function in women diagnosed with breast cancer.

Protocol

To find out the impact of RF therapy and PFMT on the perception of body self-image in women diagnosed with breast cancer.

The recruitment of breast cancer survivors will be carried out at the facilities of two associations of patients diagnosed with breast cancer in the province of Alicante: Asociación de Mujeres Afectadas por el Cáncer de Mama de Elche y Comarca (AMACMEC, Elche) and Asociación de cáncer de Mama Vinalopó (AcMAVI, Petrel). Both associations have signed a collaboration agreement with the CEU Cardenal Herrera University for the development of the study. The evaluation and intervention will be carried out at the facilities of the Department of Nursing and Physiotherapy of the Faculty of Health Sciences of the CEU Cardenal Herrera University (Elche, Spain).

Volunteers who want to participate in the study will read the general information of the study and sign the informed consent to participate in the study.

Interventions

Group 1. Treatment based on radiofrequency.

The proposed therapeutic process will consist of applying RF in the modality of capacitive electrical transfer (Capernergy® device model C500 Urogyne, Capenergy Medical, Barcelona, Spain). This is a device designed primarily for addressing dysfunctions in the urogynecological area, where the increase in tissue temperature is regulated by a temperature sensor, with 3 frequencies (0.8MHz, 1MHz and 1.2 MHz) that will allow different tissue depths to be addressed, and a power of 310w. This device consists of two electrodes: an active capacitive electrode to be placed in the vaginal area with a probe cover and water-soluble gel and another dispersive electrode or return plate to be positioned in the lumbosacral region.

The protocol to be performed is based on a previous treatment shown to be effective for the treatment of UGS in postmenopausal women45. Participants will be placed in a lithotomic position, with lower limbs flexed and supported. The treatment temperature will be set at 41°C, with a frequency of 1Mhz and power of 75KJ. Once the indicated temperature has been reached, the physiotherapist will perform semicircular movements on the vaginal wall for 2 minutes on the anterior vaginal side and for 4 minutes on the posterior vaginal wall. A total of 5 sessions will be carried out with an interval of 7 days between each one of them, for a total of 4 weeks of treatment. Patients will be instructed to contact the investigators if they experience any discomfort or notice any change in vaginal discharge.

Group 2. PFMT-based treatment

Patients in the PFMT group will be assisted during the sessions by experienced physiotherapists. PFMT will consist of a programme where the participants, in groups of 8, will perform a programme of CORE and pelvic floor exercises established based on an assessment of the patients' strength, endurance and fatigability. The aim is to activate the pelvic floor muscles in isolation and in association with the CORE muscles, both statically and dynamically.

The design of the exercise protocol and sequences is based on an adaptation of the programme described in a previous study carried out in 117 climacteric women with pelvic dysfunction, which showed significant improvement in UI symptoms, vaginal symptoms and sexual function similar to what we intend to analyse in this project, and on previous studies on therapeutic exercise in the prevention and treatment of pelvic floor pathologies based on PFMT, hypopressive technique, CORE work and the use of unstable bases.

The PFMT will take place twice a week, with each session lasting 45 minutes and a total training period of 16 weeks. The PFMT will expand goals by month and will have different sessions per week, to encourage adherence and motivation from the variability of the exercises. The first four weeks will include a first day of CORE and pelvic floor training in a cabin and individual session to ensure understanding of concepts and correct technique. After this, the therapeutic exercise protocol will focus on proprioception, mobilisation and activation of the structures responsible for the CORE, isometric work, voluntary activation of the CORE musculature, pelvic floor and synergic musculature such as the gluteus, both static and dynamic, as well as the performance of exercises in resisted expiration and apnoea to facilitate the activation of the lumbopelvic complex, as previous programmes aimed at patients with abdominopelvic dysfunctions have demonstrated their efficacy.

In the second month, mobility, proprioception and PFMT exercises facilitated by posture and breathing will be maintained, and the load will be increased with positions against gravity, activation in movement and activation against resistance of the accessory musculature.

In the third month, mobility, proprioception and PFMT exercises will be continued with an increase in load through posture and movement, and external loads will be introduced at 60% of their RM according to the progression of the loads in terms of strength, endurance and health.

In the fourth month, after reassessing the RM for load management, the load will be increased to 75% and we will focus on the work and activation of the CORE and pelvic floor in a dynamic way, with normalised breathing and introducing impact and fatigue, demonstrable risk factors in pelvic pathology. The aim is to achieve the automation of the abdominopelvic synergy and its competence in situations both in daily life and in

physical exercise.

Primary outcomes

The primary outcome will be the indication of improvement in pelvic function after the proposed interventions as assessed through the PFDI-20 questionnaire. This questionnaire allows assessment of the impact in the last 3 months of urinary symptoms (Urinary Impact Questionnaire; UIQ-7), colo-rectal-anal symptoms (Colorectal-Anal Impact questionnaire, CRAIQ-7) and genital prolapse symptoms (Pelvic Organ Prolapse Impact Questionnaire, POPIQ-7). The maximum possible score is 300 points, with a maximum value of 100 points for each subscale. The higher the score, the greater the negative impact on quality of life.

Secondary outcomes

The determinations indicated in this section will be made before starting the intervention, fifteen days after the end of the intervention, six months after the end of the intervention and twelve months after the end of the intervention.

Assessment of the strength of the pelvic floor musculature

Prior to the measurement, participants will be asked to go to the toilet to urinate, thus allowing the bladder volume to be standardised as far as possible. They will complete a resting period of 3 minutes in a seated position prior to the measurement, as this time corresponds to twice the duration of sympathetic system deactivation. For the force recording, the women will be placed in a lithotomic position, with the genital region and legs unclothed, covered by a sheet. They will then be instructed to remain relaxed.

The first examination will consist of a bidigital palpation to estimate the strength of the pelvic floor musculature during maximal contraction using the Oxford scale based on previous studies indicating the influence of strength, endurance and fatigability on pelvic floor competence and its relationship to the synergistic musculature. The Oxford scale assesses the contractile capacity of the pelvic floor muscles. It is scored from 0 to 5 as follows: no contraction is 0, very weak contraction is 1, weak contraction is 2, moderate/tension/and maintained contraction is 3, good contraction and maintaining tension with resistance is 4, and strong contraction and maintaining tension against a

resistant force is 5. In addition, this assessment allows determination of static muscular endurance, fatiguability or dynamic endurance and maximal muscular strength.

Strength and endurance will also be determined by using a pelvimeter consisting of an inflatable vaginal probe connected to the PHENIX LIBERTY therapeutic neuromuscular stimulation and manometry device (ELECTRONIC CONCEPT LIGNON INNOVATION, Montpeilier, France). The air probe, connected to the Phenix biofeedback system, covered by a latex probe cover lubricated with gel, will be used. In the procedure, the labia majora are opened with one hand and slowly rotated into the vagina by holding the back of the manometric probe with the other hand. Pelvic floor pressure signals will be collected by measuring both the basal tone of the pelvic floor and the maximum pressure maintained for 10 seconds in three measurements, with the average of the three being calculated at the command, ‘contract as hard as you can for as long as possible.

Pelvic function and quality of life

Pelvic function will be assessed with the PFDI-20 questionnaire described above, and in addition with the following questionnaires:

The International Consultation on Incontinence Questionnaire - Short Form (ICIQ-SF) is a four-question self-administered questionnaire that identifies individuals with urinary incontinence by assessing frequency, severity and impact on quality of life. It consists of five questions assessing frequency, severity and impact of UI, plus a set of eight self-diagnostic items related to UI situations experienced by patients. The maximum sum of the response values indicates a score of 21 points, referring to the high impact of UI on an individual's life.

The Sandvik severity test provides insight into the severity of UI by means of two questions. The interpretation based on the score is classified as: 1-2 mild UI, 3-6 moderate UI, 8-9 severe UI, 12 very severe UI.

Vaginal symptoms

Physical examination will assess the vaginal health index (VHI), which consists of a graded scale of 1 to 5 for each item (vaginal elasticity, fluid volume, pH, epithelial integrity and moisture). Vaginal elasticity ranges from 1 (no elasticity) to 5 (excellent elasticity), assessed by distending the mucosa on palpation and on placement of the VHI. Vaginal

elasticity ranges from 1 (no elasticity) to 5 (excellent elasticity), assessed by distension of the mucosa on palpation and speculum placement. Fluid volume, assessed during inspection, varies between 1 (no discharge) and 5 (normal discharge, white flocculent). The integrity of the epithelium ranges from 1 (petechiae already detected on inspection) to 5 (non-friable tissue and normal mucosa). Moisture ranges from 1 (no moisture detected on inspection and presence of inflamed mucosa) to 5 (normal moisture). The pH will be quantified using a pH indicator strip between 0 and 14 to be placed directly on the right lateral vaginal wall for one minute, giving 1 point for pH 6.1, 2 for pH 5.6-6.0, 3 for pH 5.1-5.5, 4 for pH 4.7-5.0 and 5 for pH ≤ 4.6. The sum of all items represents the vaginal health score, where 25 represents the best vaginal health.

Sexual function and self-esteem

The Female Sexual Function Index (FSFI) questionnaire consists of 19 items that assess sexual function over the past 4 weeks and performance in six domains: sexual desire, arousal, lubrication, orgasm, satisfaction and pain. A cut-off point ≤ 26.5 is considered sexual dysfunction and an increase in score is considered an improvement.

Dyspareunia will be assessed using the Visual Analogue Scale (VAS), which allows the intensity of pain described by the patient to be measured with maximum reproducibility between observers. It consists of a horizontal line of 10 centimetres, at the ends of which are the extreme expressions of a symptom. At the left end is the absence or lowest intensity and at the right end is the highest intensity. The patient is asked to mark on the line the point that indicates the intensity of the pain during sexual intercourse and it is measured with a millimetre ruler. The intensity is expressed in centimetres or millimetres. The rating will be: 1 Mild pain if the patient scores the pain as less than 3; 2 Moderate pain if the rating is between 4 and 7; 3 Severe pain if the rating is equal to or greater than 8.

The Body Image Scale (S-BIS) consists of 10 items assessing various dimensions of body image in cancer patients, evaluating: affective, behavioural and the items are scored on a four-point scale (0: not at all; 1: a little; 2: quite a lot; 3: a lot) with a maximum possible score of 3 points. The higher the score, the higher the body image problem. Its brevity facilitates rapid assessment in both clinical and research settings.

Baseline and follow-up period assessment

After signing the informed consent, patients will undergo an anamnesis that includes

questions related to a questionnaire designed ad hoc that will allow to know the sociodemographic characteristics, as well as information related to the diagnosis and treatment of breast cancer. They will complete the questionnaires described above on pelvic function and quality of life, vaginal health, sexual function and self-esteem. Subsequently, patients will be referred for a physical examination consisting of pelvic floor muscle strength assessment. Questionnaires will be self-completed by participants and collected at the end of the baseline assessment. These procedures will be performed at the initial assessment (first visit).

Patients will be followed up in 3 periods after the interventions: first follow-up (15 days after the intervention), second follow-up (6 months after the intervention) and third follow-up (12 months after the intervention). The same assessment procedures will be performed at follow-up as at baseline.

Data collection and management

A researcher will assist participants in completing the questionnaires and will check that all questionnaires are completed and signed. A physiotherapist with more than 15 years of pelvic floor experience will assess the pelvic floor muscle strength and vaginal health of all participants. Two physiotherapists with more than 15 years of experience in rehabilitation will perform the PFMT interventions. One physiotherapist with more than 10 years of experience will perform radiofrequency intervention.

The data collected for this study will be included in a computerised database of a personal nature of the CEU Cardenal Herrera University, to which access will only be granted to the researcher responsible for the analysis, extraction and handling of the data, by means of an access code, being subject to the secrecy inherent to their profession or derived from a confidentiality agreement.

Statistical Analysis Plan (SAP)

The Kolmogorov-Smirnov test will be used to assess the normality of the sample. Comparative analyses between groups will be performed by analysis of variance (ANOVA) or Kruskal-Wallis test. Associations of categorical variables will be analysed using the Chi-square test and Fisher's exact test. Intra-group assessment will be performed using the Wilcoxon test or Student's t-test for paired samples for continuous variables, and McNemar's test for categorical variables.

The data will also be evaluated using ANOVA for repeated measures in order to simultaneously verify the influence of the three study groups (between-group effect), the two assessments (within-group effect) and to estimate the group × time interaction effect for each of the variables. The results will be analysed by intention-to-treat. The significance level will be 5%. IBM SPSS Statistics for Windows, version 29.0 (SPSS Inc., Chicago, IL, USA) will be used.

Statistical analysis of the data collected will be performed by a researcher blinded for the intervention and for data collection.

GENERAL STUDY INFORMATION AND INFORMED CONSENT

UNIVERSITY CEU CARDENAL HERRERA

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GENERAL STUDY INFORMATION

TITLE: **Effectiveness of radiofrequency and exercise-based rehabilitation on symptoms associated with pelvic floor dysfunction in breast cancer patients**

Mrs. Cristina Orts Ruiz, Physiotherapist, principal investigator and researcher reports that: The study in which will be part of rehabilitation on symptoms associated with pelvic floor dysfunction in breast cancer patients. In this way we can contribute to promote the health status of people with this pathology.

The tests performed are simple and in no case involve difficulty, fatigue, danger, injury, pain or adverse reaction.

They will be carried out by collegiate physiotherapists in the School of Physiotherapists of the Valencian Community.

The general data of the subject will be collected (name, age, sex, physical variables and clinical history). The subject should come with comfortable clothes. The day that you were cited by the researcher, previous notice. Personal data is recognized in this study.

The personal data are confidential, apply to the protection of personal data. The study will be carried out in accordance with the Declaration of Helsinki and in accordance with current Spanish legislation (Royal Decree 223/2004 and the Biomedical Research Act 2007) and any other thing that may be applicable.

This study was approved by the Research and Ethics Committee of CEU Cardenal Herrera University (CEEI24/540).

INFORMED CONSENT

Mr/Mrs..... with Number identification .... freely and voluntarily, I DECLARE:

That I have read the information contained in this document about the general information of the study.

I have been informed that all tests are simple to perform and do not produce harmful effects on health. They will be carried out in appropriate facilities and will be carried out by qualified and specialized personnel.

I have also been informed that, the data collected in this study will be treated confidentially, applying the current legislation on protection of personal data (Royal Decree 223/2004 and the Biomedical Research Act 2007) and any other applicable.

Therefore, I give my consent, and I authorize Mrs. Cristina Orts Ruiz, to carry out the detailed study in this document with the help of the necessary personnel with the appropriate qualification and specialization.

In Elche, to ..... of ..... of 201

SIGNED