DEPARTAMENTO DE FISIOTERAPIA
FACULTAD DE CIENCIAS DE LA SALUD
UNIVERSIDAD DE GRANADA

DOLOR MUSCULOESQUELETICO EN EL CÁNCER DE MAMA. DESCRIPCIÓN Y ABORDAJE DESDE LA FISIOTERAPIA

MUSCULOSKELETAL PAIN IN BREAST CANCER. DESCRIPTION AND PHYSICAL THERAPY APPROACH

TESIS DOCTORAL EUROPEA/*EUROPEAN PhD THESIS*

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DICIEMBRE 2011

Editor: Editorial de la Universidad de Granada
Autor: Carolina Fernández Lao
D.L.: GR 513-2013
ISBN: 978-84-9028-060-7

"A Nilo, mis padres y mi hermano"

Departamento de Fisioterapia
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Que la tesis doctoral titulada: *"Dolor musculoesquelético en el cáncer de mama. Descripción y abordaje desde la Fisioterapia"* que presenta D. Carolina Fernández Lao al superior juicio del Tribunal que designe la Universidad de Granada, ha sido realizada bajo mi dirección durante los años 2009-2011, siendo expresión de la capacidad técnica e interpretativa de su autora en condiciones tan aventajadas que le hacen merecedora del Título de Doctor con mención Europea, siempre y cuando así lo considere el citado Tribunal.

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En Granada, 9 de Noviembre de 2011

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OTROS PROYECTOS RELACIONADOS

- **PROYECTO:** *E-CUIDATE: Eficacia sobre el dolor musculoesquelético de una plataforma de telefisioterapia en mujeres con cáncer de mama.* Entidad Financiadora: Fondo de Investigaciones Sanitarias. Instituto de Salud Carlos III. Investigador Principal: Manuel Arroyo Morales. (2011-2013)
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RESUMEN

Un gran número de mujeres que han recibido tratamiento quirúrgico para el cáncer de mama sufren dolor postmastectomía, aunque su mecanismo no es del todo conocido. No existen estudios que hayan investigado la hipersensibilidad al dolor mecánico en supervivientes de cáncer de mama.

El masaje es ampliamente usado por las pacientes con cáncer de mama durante las diferentes fases del proceso. Diferentes estudios han intentado probar la efectividad del masaje en diferentes síntomas relacionados con el cáncer de mama, sin embargo la evidencia sobre la efectividad del masaje en pacientes con cáncer no es concluyente.

Los objetivos principales de esta tesis fueron describir los procesos de hipersensibilidad central y periférica mediante el estudio de los umbrales de dolor a la presión y la palpación de los puntos gatillo miofasciales que caracterizan el dolor musculoesquelético en MSCM; y evaluar la efectividad de la terapia manual/masaje sobre el estado psiconeuroinmunológcio y el dolor inducido por cáncer de mama.

Un total de 81 pacientes de cáncer de mama y 44 mujeres sanas que cumplieron los criterios de inclusión, fueron involucradas en los estudios de esta tesis.

Los principales hallazgos y conclusiones fueron: a) una hipersensibilidad al dolor por presión generalizada y bilateral en pacientes con dolor postmastectomía, b) hiperalgesia generalizada al dolor por presión en mujeres que han intervenidas quirúrgicamente por cáncer de mama, sugiriendo una sensibilización central, c) la liberación miofascial puede inducir un aumento inmediato en el rango de secreción salival en supervivientes de cáncer de mama y el efecto de la liberación miofascial en la función inmunológica es modulada por la actitud positiva de la paciente hacia el masaje, d) el masaje puede inducir un inmediato incremento de la variabilidad de la frecuencia cardiaca asociada con una mejora del estado de ánimo en supervivientes de cáncer.

Nuestros hallazgos ayudan a esclarecer los mecanismos de producción del dolor postmastectomía y apoyan el uso de la terapia manual en el manejo de los síntomas asociados al cáncer de mama.

ABSTRACT

Regional or local pain is one of the most common symptoms after treatment for breast cancer. A high number of women who have received surgical treatment for breast cancer suffer post-mastectomy pain, although its mechanism is not fully understood. No studies have investigated the mechanical pain hypersensitivity in breast cancer survivors.

Massage is broadly used by patients with breast cancer during different phases of the condition; however, evidence suggesting that massage is an effective option for breast cancer patients is inconclusive. Several studies have tried to prove the effectiveness of massage on different symptoms related to treatment for breast cancer.

The overall aims of this study were to describe the characteristics of musculoskeletal pain in breast cancer survivors assessing central hypersensitivity by spontaneously occurring pain, pressure pain thresholds and myofascial trigger points, as well as to analyze the effect of manual therapy on the psychoneuroimmunological function of these patients.

A total of 81 breast cancer patients and 44 healthy women who fulfill the inclusion criteria were involved in the studies of this Thesis.

The main findings and conclusion were: a) a bilateral widespread pressure pain hypersensitivity in patients with postmastectomy pain, b) widespread pressure pain hyperalgesia in women who received breast cancer surgery suggesting central spreading sensitization, c) myofascial release may lead to an immediate increase in salivary flow rate in BCS and the effect of myofascial release on immune function was modulated by a positive patient's attitude toward massage, d) massage may lead to an immediate increase of HRV associated with a mood improvement in BCS.

This findings help to highlight the mechanism of postmastectomy pain and support the use of manual therapy techniques in the management of breast cancer symptoms.

ABREVIATURAS

OMS	Organización Mundial de la Salud
NCI	National Cancer Institute
MSCM	Mujeres Supervivientes de Cáncer de Mama
DPM	Dolor Postmastectomía
CAM	Complementary Alternative Medicine
PG	Puntos Gatillo
UDP	Umbrales de Dolor a la Presión
VFC	Variabilidad de la Frecuencia Cardiaca
IgA	Inmunoglobulina A
ATOM	Attitudes Toward Massage

ABBREVIATIONS

WHO	World Health Organization
NCI	National Cancer Institute
BCS	Breast Cancer Survivors
PMP	Postmastectomy Pain
CAM	Complementary Alternative Medicine
TrPs	Trigger points
PPT	Pressure Pain Thresholds
HRV	Heart Rate Variability
IgA	Immunoglobulin A
ATOM	Attitudes Toward Massage

INTRODUCCIÓN/INTRODUCTION

INTRODUCCIÓN

DOLOR Y CÁNCER

El cáncer es una enfermedad cuya incidencia está aumentando con el paso del tiempo y cuyo síntoma más frecuentemente registrado es el dolor, así como el más preocupante del enfermo oncológico en estado avanzado (1). Según la Organización Mundial de la Salud (OMS), al menos 3,5 millones de personas en todo el mundo sufren diariamente dolor asociado al cáncer (2). Un estudio reciente (3) que agrupó los resultados de 52 trabajos mostró que la prevalencia del dolor en pacientes con cáncer es de un 64% en pacientes con metástasis o etapa avanzada de la enfermedad, un 59% en pacientes en tratamiento contra el cáncer y el 33% en los pacientes después del tratamiento curativo. Además más de un tercio de los pacientes con dolor, según los datos de la literatura reciente, lo calificaron como moderado o grave (3).

A pesar de las claras recomendaciones (2) en cuanto a evaluación y manejo del dolor de la OMS mediante indicación de fármacos y aplicación de otros tipos de técnicas analgésicas, el dolor asociado al cáncer sigue siendo un problema importante. La mejora de los tratamientos y los avances en la investigación suponen un aumento del número de supervivientes de cáncer que viven una avanzada edad, lo cual significa que es de suma importancia reducir la prevalencia del dolor en todas las etapas del proceso de la enfermedad. Por ello, sigue siendo importante realizar estudios que nos ayuden a conocer las características y comportamiento del dolor en los diferentes tipos de cáncer con el objetivo de mejorar su abordaje terapéutico, y por tanto la calidad de vida durante y después de estos procesos. A este respecto, la fisioterapia juega un importante papel en el tratamiento y la prevención del dolor asociado al cáncer, convirtiéndose la investigación en este campo una prioridad para la comunidad científica y la sociedad.

DOLOR Y CÁNCER DE MAMA

En los Estados Unidos, el National Cancer Institute (NCI) ha estimado que un 1,09% (95% intervalo de confianza [IC] del 0.95-1,24%) de las mujeres de 30 a 84 años tiene un riesgo absoluto de padecer cáncer de mama del 20% durante la vida (4). En España, un estudio reciente encontró que desde 1980, la incidencia de cáncer de mama se ha incrementado un 2,9% al año (5). El dolor regional o local es uno de los síntomas más frecuentes después del tratamiento contra el cáncer de mama, con una prevalencia de entre 20-68% de las pacientes (6-8). Los programas de screening y los avances en los métodos diagnósticos y terapéuticos han elevado la tasa de supervivencia en los últimos años hasta casi un 70% a los 5 años después del diagnóstico (9). Existe un interés creciente sobre la mejora de los tratamientos quirúrgicos del cáncer de mama, con dos diferentes opciones quirúrgicas: mastectomía (extirpación completa de la mama) o lumpectomía (extirpación del tumor y el tejido de sus alrededores). De hecho, la lumpectomía es preferida en las pacientes más jóvenes con senos más pequeños, ya que es menos mutilante cosméticamente (10). Además, se ha encontrado que la incidencia de las complicaciones postoperatorias es superior con la mastectomía (35%) que con una lumpectomía (24%) (11).

El cáncer de mama es considerado el tipo de cáncer más común entre las mujeres (12). El dolor durante el proceso del cáncer de mama tiene una fuerte relación con el aumento de la discapacidad percibida y el descenso de la calidad de vida (13). Existen estudios que hablan sobre la interferencia del dolor con las actividades físicas y recreacionales como conducir un coche, el cuidado de los niños, el tiempo de ocio o el sexo, lo que tiene como resultado una baja percepción de la calidad de vida (14-16). De hecho, el 35% de los tratamientos quirúrgicos del cáncer de mama presentan como complicación asociada la discapacidad de hombro (12).

Además de las alteraciones funcionales, existe evidencia suficiente para considerar que la presencia de dolor antes e inmediatamente después de la cirugía es un factor predictivo de dolor crónico tras la cirugía por cáncer de mama (17). Por otro lado, las mujeres que refieren sufrir dolor asociado al tratamiento quirúrgico en el cáncer de mama tienen un mayor riesgo de estrés psicológico en comparación con aquellas pacientes que no sufren dolor (16).

Mientras que las aproximaciones basadas en juicios clínicos habían subestimado la aparición de dolor después de la cirugía por cáncer de mama hasta la década de 1990 (18), algunos estudios posteriores mostraron que gran mayoría de las mujeres supervivientes de cáncer de mama (MSCM) continúan experimentando dolor crónico y / o parestesia años después del tratamiento (6, 19-21).

Dolor Postmastectomía en el cáncer de mama

La persistencia del dolor más allá de período "normal" de curación después del proceso quirúrgico es llamada "dolor postmastectomía". Aunque su mecanismo no es del todo conocido, suele ser atribuido a diferentes causas con una mayor contribución del daño sufrido en los nervios periféricos durante la intervención quirúrgica (6, 22).

El dolor postmastectomía (DPM) es un síndrome de dolor crónico y es descrito como un dolor neuropático típico, quemazón, dolor punzante, sensación eléctrica, y suele ser provocado por la presión o bien, de forma espontánea (23). Un estudio ha referido que el 43% de las mujeres que han recibido un tratamiento quirúrgico para su cáncer de mama sufren dolor neuropático postmastectomía (6). Además del dolor debido a la hipersensibilidad de los nervios, otros tejidos también pueden estar implicados en el proceso de rehabilitación tras la cirugía. Esto incluye la debilidad muscular, la fibrosis del tejido blando, la obstrucción del flujo linfático y la hipertonía de los músculos. Este síndrome de dolor puede incluir dolor en la cicatriz quirúrgica, en la pared torácica y el brazo, molestias de hombro, sensaciones táctiles y dolor de la mama fantasma (24).

Algunos estudios han demostrado que una gestión inadecuada del dolor en el postoperatorio agudo es uno de los mayores predictores de los síndromes de dolor crónico en las pacientes tras la cirugía de la mama (25). Los síntomas son preocupantes y pueden ser difíciles de tratar, sin embargo el tratamiento no farmacológico para el dolor neuropático y para el resto de los tejidos involucrados puede ser exitoso. Por todo lo anterior, parece que hay una necesidad de ensayos clínicos que evalúen la efectividad de las terapias no farmacológicas en este síndrome doloroso. A este respecto la fisioterapia cuenta con recursos importantes para el manejo de las pacientes que sufren DPM.

Puntos Gatillo y dolor en cáncer de mama

Aunque se considera que el DPM tiene un origen neuropático (23), existe evidencia que sugiere que hay otros factores contribuyentes, como el tejido miofascial, que también puede estar implicado en el origen de este síndrome doloroso (26). En este contexto, Simons et al. (1999) sugirieron que los puntos gatillo miofasciales juegan un rol importante en el DPM (27). Los puntos gatillo (PG) se definen como nódulos hipersensibles dentro de una banda tensa muscular dolorosa a la contracción, al estiramiento o a la estimulación manual y que producen dolor referido distal al nódulo (27). Los puntos gatillo activos son aquellos que producen dolor referido y local, refiriendo los síntomas de los pacientes, siendo reconocidos como un dolor usual o familiar (27).

Sin embargo, la evidencia disponible hasta la fecha sobre la relación entre la aparición de PG miofasciales y el dolor en el pecho es escasa. Un estudio antiguo demostró que ciertas intervenciones miofasciales dirigidas a los músculos de la pared torácica proporcionan un alivio del dolor después de la tumorectomía y la radiación sobre el pecho en pacientes con cáncer de mama (28). Hamada et al. (29) documentaron una serie de casos de 27 pacientes con dolor postoracotomía, que a menudo se supone que presenta un origen neuropático, y encontraron que en el 67% de los casos la principal fuente de dolor fue el origen miofascial. Además, estos autores comentan que la existencia de los PG miofasciales aumentó significativamente la tasa de éxito después de tratamiento (29). En una cohorte de 163 pacientes con cáncer de mama, Cheville y Tchou (22) mostraron que el 21% también presentaba dolor de origen miofascial. Cummings ha descrito un caso en el cual los principales PG pectorales fueron activados como consecuencia de un traumatismo muscular después la cirugía transaxilar (30). Otro estudio mostró que las intervenciones basadas en el tratamiento a través de fisioterapia de este tipo de dolor, produce alivio de la sintomatología en la paciente después de cuadrantectomía y radioterapia en estas pacientes (28). Aunque parece que el músculo /PG miofasciales pueden estar relacionados con el DPM, no existen estudios previos que hayan explorado sistemáticamente desde esta perspectiva a la población de pacientes con cáncer de mama.

La aparición de un componente muscular como un elemento más del DPM tiene importantes implicaciones clínicas, ya que abre las puertas al abordaje terapéutico no farmacológico de este dolor. La incorporación de programas de fisioterapia para la inhibición de los PG puede ser beneficiosa para reducir el dolor y prevenir restricciones de la movilidad del hombro en el dolor DPM (31,32). Así mismo, las estrategias basadas en la mejora de la movilidad y la resistencia muscular así como el tratamiento mediante masaje de los puntos gatillo podrían reducir el uso de fármacos que son utilizados para el manejo de la sensibilización central que sufren estas pacientes.

Algometría y cáncer de mama

Existe en la literatura una creciente evidencia que sugiere que el DPM también puede estar relacionado con cambios en el aumento del estímulo nociceptivo. De hecho, en un estudio realizado por Andrykowski et al. se concluyó que la mastectomía puede aumentar el dolor experimentado en sitios distantes a través de alteraciones en los perfiles neuro-endocrinos o mediante la sensibilización del sistema nervioso central (33). Otros estudios previos confirman la aparición de procesos de sensibilización central en el DPM, ligados al incremento de la estimulación de fibras C amielínicas, de forma similar a la observada en otros tipos de dolor neuropático (34).

El daño a los nervios periféricos durante los procedimientos quirúrgicos y una posterior sensibilización parece ser un factor importante que contribuye al dolor después de la cirugía en el cáncer de mama. Sin embargo, el daño del nervio puede ser difícil o imposible de documentar en el DPM con métodos neurofisiológicos convencionales (34). A este respecto, existen diferentes pruebas sensoriales cuantitativas para valorar la presencia de mecanismos de sensibilización en enfermedades crónicas (35). Uno de los procedimientos más comunes utilizado para evaluar la hiperexcitabilidad del sistema nervioso central es el cálculo umbrales de dolor a la presión (UDP). El umbral de dolor a la presión se define como la cantidad mínima de presión que produce una sensación de cambio a dolor (36).

Varios estudios han investigado el sistema nociceptivo en diferentes condiciones crónicas mediante la evaluación de hipersensibilidad generalizada al dolor mecánico, por ejemplo, el latigazo cervical (37), la fibromialgia (38), las lesiones por esfuerzo repetitivo (39), la cefalea de tipo tensional (40), el dolor de espalda (41). Sería interesante por tanto, conocer los cambios inducidos por el tratamiento oncológico en los UDP para poder entender mejor la génesis de este tipo de síndromes dolorosos.

Como se ha visto previamente el concepto de umbral de dolor a la presión y la medición de la aparición de la sensación de dolor con el algómetro han sido foco de atención de numerosas investigaciones y ha centrado el interés, durante mucho tiempo de clínicos e investigadores. Sin embargo no existen estudios que hayan investigado la hipersensibilidad generalizada al dolor mecánico mediante la evaluación de los umbrales de dolor a la presión en MSCM. Así mismo, se desconoce si diferentes procedimientos quirúrgicos pueden estar asociados a cambios diferenciales en el proceso de sensibilización dolorosa de estos pacientes.

ROL DE LA MASOTERAPIA EN EL TRATAMIENTO DE LAS ALTERACIONES DERIVADAS DEL TRATAMIENTO DEL CÁNCER DE MAMA

El masaje es una modalidad terapéutica que incluye aspectos físicos y psicológicos (42). Las diferentes modalidades de masaje probadas en ensayos de alta calidad han demostrado ser eficaces tanto durante (43-46) como después del tratamiento del cáncer (47-50) Aunque algunas modalidades concretas, como el effleurage, no han mostrado eficacia (51).

A pesar de ser una terapia ampliamente utilizada por los pacientes con cáncer de mama durante las diferentes fases del tratamiento y la recuperación, la evidencia científica que sugiere que el masaje es una opción efectiva para las MSCM es poco concluyente (52). Una posible razón para la falta de pruebas de masaje en pacientes con cáncer de mama, puede ser que existen muy pocos estudios que investiguen los efectos a corto plazo del masaje en esta población (52) o que tengan en consideración los potenciales factores moduladores de la respuesta psicofisiológica del masaje como las actitudes o preferencias del terapeuta y/o del paciente frente a los diferentes recursos disponibles.

Eficacia del masaje en los síntomas asociados al cáncer de mama

Entre los recursos con los que cuenta la fisioterapia es de especial interés para este grupo particular de pacientes el uso de masoterapia que ha mostrado enorme eficacia en procesos oncológicos, especialmente en la emesis asociada al tratamiento con quimioterapia (53, 54). Por otro lado, la masoterapia se postula como una técnica idónea y eficaz para tratar el dolor musculoesquelético que presentan estas pacientes durante todo el proceso de tratamiento y postratamiento del cáncer de mama. Si bien no existen estudios previos que hayan mostrado la eficacia de la masoterapia frente al DPM.

Existen varios estudios que han intentado probar la eficacia del masaje ante los diferentes síntomas relacionados con el tratamiento por el cáncer de mama. Moyer et al. realizaron un metanálisis en que estudiaron los efectos analgésicos del masaje, y hallaron que dicha técnica disminuye el dolor (42), lo que puede justificar su elevada aceptación y uso dentro de la sociedad. Por otro lado, la reflexología ha demostrado ser eficaz para disminuir el dolor en pacientes con cáncer (55-56), pero sólo un ensayo clínico aleatorio previo ha sugerido un efecto del masaje sobre el dolor corporal en pacientes con cáncer de mama (57). Jane et al han postulado recientemente sobre los efectos positivos del masaje analgésico en diferentes procesos oncológicos (58), mientras que Sturgeon et al. informaron que no hubo efectos (46). La evidencia científica sobre la capacidad analgésica de la masoterapia en el dolor oncológico es controvertida, existiendo estudios a favor y otros en contra. La necesidad de nuevos estudios favorecerá el desarrollo posterior de metanálisis que faciliten la elección de una adecuada estrategia terapéutica frente a este tipo de dolor.

La liberación miofascial es una modalidad específica de masaje basada en la manipulación del tejido miofascial para tratar alteraciones funcionales. Algunos estudios han demostrado que la aplicación de técnicas de liberación miofascial, proporciona efectos de hipoalgesia en diferentes condiciones (59,60). De hecho, los pacientes aseguran que sienten que la terapia mediante masaje produce una relajación muscular y reduce la tensión (61). Es posible que las técnicas miofasciales puedan disminuir la hipersensibilidad del dolor a la presión en supervivientes de cáncer de mama, pero ningún estudio ha investigado previamente esta hipótesis. Las discrepancias entre las revisiones ratifican la necesidad de llevar a cabo más estudios sobre este tema, que aclaren la visión de la comunidad científica y clínica sobre este modo de abordaje de los pacientes.

Existe en la literatura una amplia evidencia que sugiere que la terapia física, especialmente el ejercicio (62) y el masaje (63) son beneficiosos para mejorar la función física en MSCM. De hecho, han sido desarrolladas recomendaciones concretas sobre los programas de ejercicio en estas pacientes. (64). Todo lo cual, parece que apoya la idea de integrar la terapia física mediante ejercicio en el tratamiento de estas pacientes. Una vida sedentaria puede inducir ciertos cambios en el sistema nervioso, lo que altera el estado de percepción, disminuyendo la capacidad de hacer ejercicio y de realizar actividades de la vida diaria (65) Un estudio previo mostró que el masaje redujo la actividad parasimpática, medida por la variabilidad de la frecuencia cardíaca (VFC), lo cual fue un factor predictivo de la evolución del estado de ánimo después de la privación de las actividades usuales de ejercicio (66), lo cual suele acontecer en los pacientes oncológicos que sufren fatiga asociada al cáncer. Sería esperable que la mejora en la regulación autonómica inducida por el masaje se asociara con una mejoría en la fatiga asociada al cáncer y el estado de ánimo en las MSCM.

Por otro lado, la liberación miofascial ha demostrado la capacidad de mejorar la recuperación después del ejercicio, la fatiga provocada por la creciente variabilidad del ritmo cardíaco (67), y mejorar el estado de ánimo (68) en los sujetos sanos. Estos resultados han sido replicados en pacientes con cefalea tensional crónica (69). Sería de esperar que puedan inducirse similares cambios psico-fisiológicos inmediatos en las MSCM que sufren dolor y fatiga relacionados con el cáncer de mama, después del tratamiento de liberación miofascial.

En un entorno de cáncer, el masaje también ha demostrado tener efectos en el sistema inmunológico mediante un aumento en el número de linfocitos (70) y natural killers (51) tras su aplicación. Sin embargo, un estudio reciente no ha confirmado la mejora de la función inmune inducida por el masaje (49). Es interesante destacar que los cambios en la función inmune mediante el análisis de los marcadores de la saliva como la inmunoglobulina A (IgA) o actividad de α-amilasa han sido estudiados previamente en otro tipo de poblaciones (68, 71), pero no en MSCM. La concentración de cortisol y de la actividad α-amilasa son marcadores de respuesta al estrés que están alterados en estas mujeres (72). Sería interesante investigar cambios en el sistema inmunológico en MSCM después de la aplicación de técnicas de liberación miofascial para ratificar la generalización de los efectos en pacientes oncológicos.

Influencia de las expectativas de los pacientes frente al efecto de la masoterapia

Cualquier fisioterapeuta con una trayectoria clínica dilatada ha percibido la respuesta diferente al mismo tratamiento, manifestada por pacientes con un perfil psicológico distinto. Sin embargo, existe un gran vacío en la investigación relacionada con la influencia de las actitudes de los pacientes sobre el resultado clínico de la fisioterapia, especialmente en un recurso tan utilizado como el masaje (42). A este respecto Moyer y Rounds desarrollaron una herramienta que evalúa los efectos del masaje según la influencia de las creencias del pacientes, la escala ATOM (Attitudes Toward Massage) (73). Es posible que la experiencia previa o la esperanza de los pacientes hacia la terapia de masaje puedan modular los efectos del masaje. La creencia es que las supervivientes de cáncer de mama que tengan una actitud positiva hacia el masaje serán más propensas a experimentar una mayor mejoría que aquellos con una actitud negativa.

Por último, parece que la experiencia de los síntomas del cáncer como el dolor es el resultado de la el procesamiento complejo de información que se transmite al cerebro desde la periferia sensorial y otros aspectos como el procesamiento cognitivo y emocional (74). Curiosamente, una de las razones más frecuentemente postulada para el uso de las diferentes formas de medicina complementaria alternativa en las supervivientes de cáncer de mama es fortalecer el sistema inmunológico y mejorar la capacidad de relajar los músculos en el área de dolor (75). Este tipo de creencia y actitud de las pacientes hacia una modalidad terapéutica, como la liberación miofascial puede influir en los efectos de esta intervención terapéutica.

Por lo que sabemos no existen estudios anteriores que hayan investigado el efecto de modulación de la actitud de los pacientes hacia la liberación miofascial y el masaje en MSCM sobre síntomas como el dolor, la fatiga o la función del sistema inmune, por lo que sería de interés profundizar en este aspecto con estudios de investigación rigurosos. Dichos estudios ayudarían al entendimiento de los mecanismos de acción de ciertas terapias no farmacológicas, tan demandadas por los propios pacientes, sobre los problemas específicos que presentan las MSCM.

INTRODUCTION

PAIN AND CANCER

Cancer incidence is increasing over time and its most frequently reported symptom is pain, and the most worrisome in advanced cancer patients (1). According to the World Health Organization (WHO), at least 3.5 million people worldwide have daily pain associated with cancer (2). A recent study (3) which pooled the results of 52 papers showed that the prevalence of pain in cancer patients is 64% in patients with metastasis or advanced disease stage, 59 % in patients with cancer treatment and 33% in patients after curative treatment. In addition, more than a third of patients with pain in the articles reviewed described it as moderate or severe (3).

Despite the clear recommendations of WHO (2) regarding pain assessment and management, by indicating application of drugs and other analgesic techniques, the pain associated with cancer remains a major problem. Improved treatments and research advances imply an increasing number of cancer survivors living an advanced age, which means that it is very important to reduce the prevalence of pain in all stages of the disease. So is very important to conduct studies that help us understand the characteristics and behavior of pain in different types of cancer with the aim of improving the quality of life during and after these processes. In this regard, physiotherapy plays an important role in treating and preventing pain associated with cancer, making research in this area a priority for the scientific community and general society.

PAIN AND BREAST CANCER

In the United States, the National Cancer Institute (NCI) has estimated that 1.09% of women aged 30 to 84 years had a lifetime absolute breast cancer risk of 20% which translates to 880,063 U.S. women (4). A recent study found that since 1980 the incidence of breast cancer increased by 2.9% per year in Spain (5). Regional or local pain is one of the most common symptoms after treatment for breast cancer, with a prevalence of 20-68% of patients (6-8) and a strong relationship with perceived disability and quality of life (9).Screening programs and advances in therapeutic and diagnostic approaches have raised survivor rate in last years close to 70% at 5 years of diagnosis (4). There has been an increasing interest for improving surgical treatments for breast cancer, with two current different surgical options: mastectomy (whole breast removed) or lumpectomy (tumor and surrounding tissue removed). In fact, lumpectomy surgery is preferred in younger patients with smaller breasts, as it is less cosmetically mutilating (10). Additionally, the incidence of postoperative complications has been found to be higher with mastectomy (35%) than with lumpectomy (24%) procedures (11).

Breast cancer is considered the most common cancer among women (12). Pain during breast cancer has a strong relationship with the increase in perceived disability and decreased quality of life (13). There are studies about pain interference with physical and recreational activities such as driving a car, childcare, leisure time or sex practice, which results in a low perceived quality of life (14-16). In fact, 35% of surgical treatments of breast cancer have shoulder disability as associated complication (12).

In addition to functional disorders, there is a wide evidence to believe that the presence of pain before and immediately after surgery is a predictor of chronic pain after breast cancer surgery (16). On the other hand, women who report having pain after surgery following a mastectomy have a higher risk of psychological distress compared with those patients without pain (16).

While the approaches based on clinical trials underestimated the occurrence of pain after breast cancer surgery until the 1990s (18) some studies showed that a large majority of breast cancer survivors (BCS) suffer chronic pain and / or paresthesia years after treatment (6, 19-21).

Postmastectomy Pain in breast cancer

The persistence of pain beyond the period of "normal" healing following surgical process is called "post-mastectomy pain." Although its mechanism is not fully understood it is often attributed to different reasons with a larger contribution from the damage to peripheral nerves during surgery (6, 22).

Postmastectomy pain (PMP) is a chronic pain syndrome, usually described as a typical neuropathic pain, burning, stabbing, electric feeling, and is usually caused spontaneously or by applying pressure (23). A study has reported that 43% of women who have received surgical treatment for breast cancer suffer post-mastectomy neuropathic pain (6). In addition to pain due to hypersensitivity of the nerves, other tissues may also be involved in the rehabilitation process after surgery. These include muscle weakness, soft tissue fibrosis, obstruction of lymph flow and muscle hypertonia. This pain syndrome may include pain in the surgical scar, chest wall and arm, shoulder discomfort and tactile sensations and phantom breast pain (24).

Some studies have also shown that inadequate management of acute postoperative pain is one of the greatest predictors of chronic pain syndromes in patients after breast surgery (25). Symptoms are disturbing and may be difficult to treat. However, treatment for neuropathic pain and for the rest of the tissues involved can be successful. For all the above, it seems that there is a need for clinical trials that will evaluate the effectiveness of “non pharmacologic” therapies or consider "complementary alternative medicine" (CAM) in this painful condition. In this regard, the physiotherapy has important resources for the management of patients with PMP.

Trigger Points and pain in breast cancer.

Although it is considered that the PMP has a neuropathic origin (23), there is evidence to suggest that there are other contributing factors such as myofascial tissue, which may also be involved in the origin of this pain syndrome (26). In this context, Simons et al. (1999) suggested that myofascial trigger points play an important role in the PMP (27). Trigger points (TrPs) are defined as hypersensitive nodules within a taut band, that can be painful with muscle contraction, stretching or manual stimulation and can produce referred pain distal to the nodules (27). Active TrPs are those that produce local and referred pain, referring to the symptoms of patients, being recognized as a usual or familiar pain (27).

However, evidence analyzing the relationship between muscle TrPs and chest pain is scarce. An old study showed that myofascial interventions targeted to the chest wall muscles provide pain relief after lumpectomy and radiation in breast cancer patients (28). Hamada et al. (29) document a case series of 27 patients with post-thoracotomy pain, which is often assumed to be neuropathic in origin, and found the primary source of pain to be myofascial in 67%. Furthermore, these authors commented that the existence of muscle TrPs significantly increased the rate of success after treatment (29). In a cohort of 163 breast cancer patients, Cheville and Tchou (22) showed that 21% also showed myofascial pain. Cummings described a case report in which pectoralis major TrPs were activated as a result of muscle trauma after transaxillary surgery (30) Although it seems that muscle/myofascial TrPs can be related to PMP, no previous study has systematically explored them in this patient population.

The existence of a muscular component as an element of the PMP has important clinical implications, as it opens the door to non-pharmacological therapeutic approach of this pain. The addition of physical therapy programs for the inhibition of TrPs can be beneficial in reducing pain and mobility restrictions, preventing shoulder pain in PMP (31, 32). Likewise, strategies based on improving mobility and muscle strength as well as treatment by massage of trigger points could reduce the drug use employed for managing the patients' central sensitization suffering.

Pressure pain threshold and breast cancer

There is increasing evidence suggesting that PMP may be also related to changes in nociceptive pain gain. Indeed, Andrykowski et al. found in a previous study that mastectomy may intensify the experience of pain at distant sites via alterations in neuro-endocrine profiles or by sensitizing the central nervous system (33). Gottrup et al. found in 15 women with PMP and abnormal sensitivity that ongoing C-fiber inputs can induce a central sensitization state similar to that seen in other pain patient populations (34).

Damage to peripheral nerves during operative procedures and subsequent sensitization appears to be an important factor contributing to pain following breast cancer surgery. However, nerve damage may be difficult or impossible to document in PMP with conventional neurophysiological methods (34). In this regard, there are several quantitative sensory tests proposed for investigating the presence of sensitization mechanisms in chronic conditions (35). One of the most common procedures used for evaluating the hyperexcitability of the central nervous system is calculating the pressure pain thresholds. Pressure pain threshold (PPT) is defined as the minimal amount of pressure where a sensation of pressure first changes to pain (36).

Several studies have investigated the nociceptive system in different chronic conditions by assessing widespread mechanical pain hypersensitivity, e.g., whiplash (37), fibromyalgia (38), repetitive strain injury (39), tension type headache (40), low back pain (41). Therefore, it would be interesting knowing the changes induced by cancer treatment in the PPT for a better understanding of the genesis of this type of pain syndromes.

As seen previously, the concept of PPT and the measurement of the onset of pain sensation using the algometer have been the focus and attention of much research and interest among clinicians and researchers for a long time. However, no studies have investigated the mechanical pain hypersensitivity by evaluating PPT in breast cancer survivors. Also, it is unknown whether different surgical procedures may be associated with different changes in the process of painful sensitization of these patients.

EFFECTIVENESS OF MASSAGE IN BREAST CANCER

Massage is a therapeutic modality including physical and psychological aspects (42). Different modalities of massage tested in high quality trials have shown to be effective during (43-46) and after (47-50) cancer treatment; however, some types of massage, like effleurage have not shown to be effective (51) .

Despite the fact that massage is broadly used by patients with breast cancer during different phases of the condition; however, evidence suggesting that massage is an effective option for BCS is inconclusive (52). One possible reason for the lack of evidence for massage in patients with breast cancer may be that there are only few studies and anecdotal information investigating short-term effect of massage in this population (52). Another reason could be the lack of studies that take account of potential modulating factors in psychophysiological response of massage as the therapist's and patient's attitudes or preferences from different therapeutic resources.

Effectiveness of massage on symptoms associated with breast cancer

Among the resources available to physical therapy, the use of massage has special interest to this particular group of patients as it has shown great effectiveness in oncological processes, especially in the emesis associated with chemotherapy (53, 54). In addition, massage therapy is offered as a suitable and effective technique to treat musculoskeletal pain of these patients during the whole process of treatment and after care of breast cancer. However, there are no previous studies that have shown the effectiveness of massage therapy in PMP.

Several studies have tried to prove the effectiveness of massage on different symptoms related to treatment for breast cancer. Moyer et al. have discussed the analgesic effects of massage in a meta-analysis and found that massage decreases pain (42). In addition, reflexology has proved to be effective for decreasing pain in patients with cancer (55-56), but only one previous randomized clinical trial has suggested an effect for whole body massage in bodily pain in patients with breast cancer (57). Jane et al. have recently postulated positive analgesic effects of massage in different oncology processes (58), while Sturgeon et al. reported no effects (46). The scientific evidence on the analgesic capacity of massage therapy for cancer pain is controversial. There is a need to carry out studies that promote the further development of meta-analysis to facilitate the choice of appropriate therapeutic strategies.

Myofascial release is a specific form of massage based on the myofascial tissue manipulation to treat functional disorders. Some studies have demonstrated that the application of myofascial release exerts hypoalgesic effects in different conditions (59,60). In fact, patients feel that massage therapy produces relaxation and reduces muscle tension (61). It is possible that myofascial techniques may decrease pressure pain hypersensitivity in breast cancer survivors; but no study has previously investigated this hypothesis. Discrepancies between reviews support the necessity for conducting more studies on this topic clarifying the point of view of the scientific and clinical community about this approach to patients.

Literature contains a wide selection of evidence suggesting that physical therapy, including exercise (62) and massage (63) are beneficial for improving physical function in BCS. In fact, specific recommendations have been developed for exercise programs for these patients. (64). All of this seems to support the idea of integration of physical therapy using exercise in the treatment of these patients. One main contributor to cancer related fatigue is sedentary habits induced by changes in the nervous system, which alters the perceptual state by decreasing the ability to exercise or the functional life activities (65). A previous study showed that reduced parasympathetic activity, as measured by heart rate variability (HRV), was predictive of the development of negative mood after deprivation of usual exercise activities (66), which often occur in cancer patients who suffer from cancer related fatigue. It would be expected that improvement in autonomic regulation induced by massage could be associated with improvements on fatigue and mood in BCS.

On the other hand, myofascial has shown the ability to improve recovery after exercise-induced fatigue, by increasing heart rate variability (67) and improving mood state (68) in healthy subjects. These results have been replicated in patients with chronic tension type headache (69). It would be expected that similar immediate psycho-physiological changes may be induced in breast cancer survivors suffering cancer related fatigue after myofascial release treatment.

In a cancer context, massage has also shown effects within the immune system as an increase in the number of lymphocytes (70) and natural killer cells (51) has been found after its application. However, a recent study has not confirmed the improvement of immune function induced by massage (49). It is interesting to note that changes in immune function by analyzing salivary markers such as Immunoglobulin A (IgA) or α-amylase activity have been previously studied in other populations (68,71), but not in BCS. Cortisol concentration and α-amylase activity are markers of stress response which are altered in these patients (72). It would be interesting to investigate changes in immune system in BCS after the application of myofascial release to confirm the widespread effects in cancer patients.

Influence of patients' expectations on the effect of massage therapy

Any therapist with a long clinical course has received different responses to the same treatment shown by patients with different psychological profile. Nevertheless, there is a lack of studies analyzing the influence of patient's beliefs and attitudes towards massage (42). In this regard Moyer & Rounds have developed a tool for evaluating the effects of massage according to the influence of the beliefs of patients, the ATOM (Attitudes Toward Massage) scale (73). It is possible that previous experience or expectancy of patients towards massage therapy can modulate the effects of massage. We postulated that BCS who had a positive attitude toward massage would be more likely to experience greater improvements than those with a negative attitude.

Finally, it seems that the experience of cancer symptoms as pain is a result of the complex processing of information relayed to the brain from the sensory periphery and other aspects such as cognitive and emotional processing (74). Interestingly, one of the most frequently postulated reasons for the use of different forms of complementary alternative medicine in breast cancer survivors is to strength the immune system and improves the ability to relax muscles within the pain area (75).

To the best of the authors' knowledge, no previous studies have investigated the influence of patients` attitude about myofascial release and massage on symptoms such as pain, fatigue and immune function in BCS. Therefore, it might be interesting to carry out further rigorous research studies in this aspect. Such studies would help in understanding about action mechanisms of some non-pharmacological therapies, demanded by patients, on the specific problems presented by BCS.

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OBJETIVOS/AIMS

OBJETIVOS

Generales:

- Describir los procesos de hipersensibilidad central y periférica mediante el estudio de los umbrales de dolor a la presión y palpación de los puntos gatillo miofasciales que caracterizan el dolor musculoesquelético en MSCM.

- Evaluar la efectividad de la terapia manual/masaje sobre el estado psiconeuroinmunológcio y el dolor inducido por cáncer de mama.

Específicos:

- Describir la presencia de hiperalgesia generalizada a la presión y existencia de PG miofasciales en los músculos del cuello y hombro en pacientes con DPM; y evaluar la relación entre los PG activos, la intensidad del dolor y los UDP en pacientes con dolor neuropático postmastectomía. **(Artículo I)**

- Investigar las diferencias en hiperalgesia generalizada a la presión tras dos modalidades diferentes de cirugía para el tratamiento del cáncer de mama: mastectomía y lumpectomía. **(Artículo II)**

- Evaluar la influencia de la actitud de las pacientes hacia el masaje en la hipersensibilidad a la presión y los efectos sobre la función inmunológica de la liberación miofascial en MSCM. **(Artículo III)**

- Investigar los efectos inmediatos de la liberación miofascial en la VFC y el estado de ánimo y la influencia de la actitud hacia el masaje en MSCM fatigadas. **(Artículo IV)**

AIMS

Overalls:

- To describe central and peripheral hypersensitivity processes through the study of pressure pain thresholds and palpation of myofascial trigger points that characterize the BCS musculoskeletal pain.

- To evaluate the effectiveness of manual therapy / massage on the psychoneuroimmunological status and pain induced by breast cancer.

Specifics:

- To describe the presence of widespread pressure pain hyperalgesia and myofascial TrPs in neck and shoulder muscles in patients with PMP; and to assess the relationship between active TrPs, intensity of the pain and PPTs in patients with postmastectomy neuropathic pain. **(Paper I)**

- To investigate the differences in widespread pressure pain hypersensitivity after two surgery approaches for breast cancer: mastectomy or lumpectomy. **(Paper II)**

- To evaluate the influence of patient's attitudes toward massage on pressure pain sensitivity and the immune effects of myofascial release in breast cancer survivors (BCS). **(Paper III)**

- To investigate the immediate effect of myofascial release on heart rate variability and mood state, and the influence of attitude towards massage in BCS with cancer-related fatigue. **(Paper IV)**

METODOLOGÍA/METHODOLOGY

METODOLOGÍA/METHODOLOGY

Se incluye un resumen de la metodología utilizada en los artículos que componen esta Tesis en la **Tabla 1.**

A summary of the methodology used in the manuscripts included in the current PhD Thesis is presented in **Table 1**.

Table 1. Summary of the methodology used in the manuscripts included in the PhD Thesis.

PAPER	STUDY DESIGN	PARTICIPANTS	INTERVENTION	MAIN VARIABLES STUDIED	METHODS
I. Myofascial Trigger Points in Neck and Shoulder Muscles and Widespread Pressure Pain Hypersensitivtiy in Patients With Postmastectomy Pain. Evidence of Peripheral and Central Sensitization	Cross-sectional blinded study (case-control)	29 BCS (with PMP) 23 healthy women (control)	Not applicable	Spontaneous neck, axillary/shoulder pain Pain distribution PPT index (C5-C6 zygapophyseal joint, deltoid muscle, second metacarpal, and tibialis anterior muscle) TrPs (upper trapezius, sternocleidomastoid, levator scapulae, suboccipital, scalene, infraspinatus, and pectoralis major muscles)	11-point Numerical Point Rate Scale Body Map Bilaterally explored with algometer (applied at approximately rate of 30 kPa/second by a 1 cm2 probe) Bilaterally manual examination
II. Widespread Mechanical Pain Hypersensitivity as a Sign of Central Sensitization after Breast Cancer Surgery: Comparison between Mastectomy and Lumpectomy	Cross-sectional blinded study (case-control)	21 BCS (lumpectomy surgery) 21 BCS (mastectomy surgery) 21 healthy women (control)	Not applicable	Spontaneous neck, axillary/shoulder pain PPT index (C5-C6 zygapophyseal joint, deltoid muscle, second metacarpal, and tibialis anterior muscle)	11-point Numerical Point Rate Scale Bilaterally explored with algometer (applied at approximately rate of 30 kPa/second by a 1 cm2 probe)
III. The influence of patient attitude towards massage on pressure pain sensitivity And immune system after application of myofascial release in breast cancer survivors: a randomized controlled crossover study	Randomized single-blind placebo-controlled crossover design	20 BCS Experimental group (n=20) Control group (=20)	Manual Therapy session (experimental group) Placebo intervention (control group) 1 week wash-up period	PPT index (C5-C6 zygapophyseal joint, temporalis muscle Attitudes Toward Massage Salivary flow rate Cortisol, IgA , α-amylase secretion	Bilaterally explored with algometer (applied at approximately rate of 30 kPa/second by a 1 cm2 probe) ATOM scale (2 Subscales, attitudes of Massage as Healthful (ATOM-MH) and Massage as Pleasant (ATOM-MP) 3 minutes saliva samplimg (passive drooling technique) Determination by luminescence

PAPER	STUDY DESIGN	PARTICIPANTS	INTERVENTION	MAIN VARIABLES STUDIED	METHODS
IV. Attitude towards massage modify effects of myofascial release in breast cancer survivors: A randomized clinical trial with crossover design	Randomized single-blind placebo-controlled crossover design	20 BCS Experimental group (n=20) Control group (=20)	Manual Therapy session (experimental group) Placebo intervention (control group) 1 week wash-up period	HRV Mood State Attitudes Toward Massage	Holter ECC recordings supine position (SDNN, RMSSD, Index HRV, LF, and HF) POMS questionnaire (8 domains: tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, confusion) ATOM scale (2 Subscales, attitudes of Massage as Healthful (ATOM-MH) and Massage as Pleasant (ATOM-MP)

BCS: Breast Cancer Survivors; PMP: Postmastectomy Pain; PPT: Pressure Pain Threshold; TrPs: Triggers Points; ATOM: Attitudes Toward Massage; HRV: Heart Rate Variability; ECC: Electrocardiogram.

RESULTADOS Y DISCUSIÓN/RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

Los resultados y la discusión de la tesis se incluyen en los artículos específicos. Se han incluido en la forma en la que han sido publicados o submitidos.

The results and discussion of the current PhD Thesis are shown as specific papers. They are enclosed in the form they have been published or submitted.

PAPER I

Myofascial trigger points in neck and shoulder muscles and widespread pressure pain hypersensitivity in patients with postmastectomy pain. Evidence of peripheral and central sensitization

Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-las-Peñas C, Del-Moral-Ávila R, Arendt-Nielsen L, Arroyo-Morales M.

Clin J Pain

Journal Citation Reports Area
Clinical Neurology: 54/185 Q2

2010 Nov-Dec;26(9):798-806

Myofascial Trigger Points in Neck and Shoulder Muscles and Widespread Pressure Pain Hypersensitivtiy in Patients With Postmastectomy Pain

Evidence of Peripheral and Central Sensitization

Carolina Fernández-Lao, PT, MSc, Irene Cantarero-Villanueva, PT, MSc,* César Fernández-de-las-Peñas, PT, MSc, PhD,† ‡§ Rosario Del-Moral-Ávila, MD,‖ Lars Arendt-Nielsen, DMSc, PhD,§ and Manuel Arroyo-Morales, MD, PT, PhD**

Objective: To describe the presence of widespread pressure pain hyperalgesia and myofascial trigger points (TrPs) in neck and shoulder muscles in patients with postmastectomy pain.

Methods: Twenty-nine women (mean age: 50 ± 8 y) with postmastectomy pain and 23 matched healthy controls (mean age: 50 ± 9 y) participated. Pressure pain thresholds (PPT) were bilaterally assessed over the C5-C6 zygapophyseal joint, the deltoid muscle, the second metacarpal, and the tibialis anterior muscle. TrPs in the upper trapezius, suboccipital, levator scapulae, sternocleidomastoid, scalene, infraspinatus, and pectoralis major muscles were explored. TrPs were considered active if the local and referred pain reproduced symptoms and the patient recognized the pain as familiar.

Results: Twenty-five (86%) patients reported neck pain whereas 20 (69%) patients showed shoulder/axillary pain. The results showed that PPT levels were significantly decreased bilaterally over the C5-C6 zygapophyseal joint, deltoid muscle, second metacarpal, and tibialis anterior muscle in patients with postmastectomy pain as compared with controls (all sites, $P < 0.001$). No significant differences in the magnitude of PPT decrease between sites were found ($P = 0.222$). The mean number of active TrPs for each woman with postmastectomy pain was 5.4 ± 1.8. Healthy controls only had latent TrPs (0.5 ± 0.6). Patients with postmastectomy pain showed a greater number of TrPs than controls ($P < 0.001$). In all muscles, there was significantly more active TrPs in patients with postmastectomy pain as compared with controls ($P < 0.001$). Active TrPs in the pectoralis major (n = 27, 93%), infraspinatus (n = 23, 79%), and upper trapezius (n = 19, 65%) muscles were the most prevalent in the affected side in the postmastectomy group. The number of active TrPs was positively correlated with neck ($r_s = 0.392$, $P = 0.036$) and shoulder/axillary ($r_s = 0.437$, $P = 0.018$) pain intensity.

Conclusions: Our findings revealed bilateral widespread pressure pain hypersensitivity in patients with postmastectomy pain. In addition, the local and referred pain elicited by active TrPs reproduced neck and shoulder/axillary complaints in these patients. These results suggest peripheral and central sensitization in patients with postmastectomy pain.

Key Words: postmastectomy pain, trigger points, pressure pain, sensitization

(*Clin J Pain* 2010;26:798–806)

Breast cancer is the most common form of cancer among women.[1] A recent study found that since 1980, the breast cancer incidence rate has increased by 2.9% per year in Spain.[2] Further, with increasing longevity and effective therapies, the population of cancer survivors also increases. For instance, it is estimated that there are 2 millions of breast cancer survivors in the United States.[3] Screening programs and advances in therapeutic and diagnostic approaches raised survivors to close to 70% 5 years after diagnosis[4]

Regional or localized pain is the most frequent impairment after breast cancer treatment (20% to 65%),[5] with a strong relationship to self-perceived disability and quality of life.[6] In fact, shoulder disability seems to be a frequent complication to the treatment of breast cancer (35%).[7] The presence of persistent pain beyond the period of "normal" healing after mastectomy surgery is called "postmastectomy pain" and it is generally attributed to the damage of peripheral nerves during the operative procedure.[8] Further, the pain is neuropathic in character as it is described as burning, electric shock-like, or stabbing.[9] A retrospective study found a prevalence of 43% of postmastectomy neuropathic pain in a sample of 408 women who had received mastectomy surgery.[10] Finally, the presence of pain before and soon after the surgery is a mayor predictive factor for chronic pain after breast surgery.[11]

There is increasing evidence suggesting that postmastectomy pain can also be related to other sources different from nerve injury, such as myofascial tissue.[12] In this context, Simons et al[13] suggested that muscle/myofascial trigger points (TrPs) can play an important role in postmastectomy pain. TrPs are defined as hyperirritable tender spots in a taut band of a skeletal muscle that are

Received for publication March 9, 2010; revised April 6, 2010; accepted April 9, 2010.
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painful on contraction, stretching, or manual stimulation and give rise to a referred pain distant from the spot.[13] Active TrPs are those which both their local and referred pains reproduce patient's symptoms and are recognized as familiar and usual pain.[13] Latent TrPs have similar examination findings as active TrPs but they do not cause spontaneous pain symptoms.[13] Clinical distinction between active and latent TrPs is substantiated by histochemical findings because higher levels of algogenic substances and chemical mediators (ie, bradykinin, substance P, or serotonin) have been found in active TrPs as compared with latent TrPs and non-TrPs.[14,15]

Evidence analyzing the relationship between muscle TrPs and chest pain is scarce. An old study showed that myofascial interventions targeted to the chest wall muscles provide pain relief after lumpectomy and radiation in breast cancer patients.[16] Hamada et al[17] document a case series of 27 patients with postthoracotomy pain, which is often assumed to be neuropathic in origin, and found the primary source of pain to be myofascial in 67%. Further, these authors commented that the existence of muscle TrPs significantly increased the rate of success after treatment.[17] In a cohort of 163 breast cancer patients, Cheville and Tchou[18] showed that 21% also showed myofascial pain. Cummings described a case report in which pectoralis major TrPs were activated as a result of muscle trauma after transaxillary surgery.[19] Although it seems that muscle/myofascial TrPs can be related to postmastectomy pain, no previous study has systematically explored them in this patient population.

Indeed, preliminary evidence suggests that mastectomy may even enhance the experience of pain at distant sites presumably via alterations in neuroendocrine profiles or direct sensitizing effects on the central nervous system.[20] In fact, Gottrup et al[21] found, in 15 women with postmastectomy pain and abnormal sensitivity, that ongoing C-fiber inputs can induce a central sensitization state similar to that seen in other pain patient populations. Nevertheless, to the best of the authors' knowledge, there are no studies investigating the presence of muscle TrPs and widespread pressure pain hypersensitivity in patients with postmastectomy pain.

The aims of this study were: (1) to describe the differences in the presence of TrPs in the upper trapezius, sternocleidomastoid, suboccipital, levator scapulae, scalene, pectoralis major, and infraspinatus muscles between patients with postmastectomy pain and healthy controls; (2) to investigate the presence of widespread pressure pain hyperalgesia in patients with postmastectomy pain; and (3) to assess the relationship between active TrPs, intensity of the pain and pressure pain thresholds (PPTs) in patients with postmastectomy neuropathic pain.

MATERIALS AND METHODS

Participants

Patients were recruited from the Department of Oncology at the Hospital Virgen de las Nieves, Granada, Spain. To be eligible for the study, participants fulfilled the following criteria: (1) had received a simple mastectomy or quadrantectomy and included those with breast reconstruction at the time of initial surgery or subsequent breast reconstruction, (2) adults at least 18 years of age, (3) first time primary diagnosis of breast cancer (grades I to IIIA), (4) postmastectomy for at least 6 months without current sign of recurrence, (5) at least 3 months after postprimary adjuvant treatment (radiation, cytotoxic chemotherapy), and (6) neck and shoulder/axillary pain that began after the breast cancer surgery. Exclusion criteria included: (1) breast surgery for cosmetic reasons or prophylactic mastectomy, (2) other medical conditions (ie, arthritis), (3) presence of lymphoedema, (4) recurrent cancer, or (5) previous diagnosis of fibromyalgia syndrome[22]

In addition, age-matched right-handed controls were recruited from volunteers who responded to a local announcement and were excluded if they exhibited a history of neck, shoulder or arm pain, history of trauma, or diagnosis of any systemic disease. The study protocol was approved by the local Ethics Committee (FIS 08-ETES-PI0890418) and conducted following the Helsinki Declaration. All participants signed an informed consent before their inclusion.

Muscle TrP Examination

TrPs were bilaterally explored within the upper trapezius, sternocleidomastoid, suboccipital, levator scapulae, scalene, pectoralis major, and infraspinatus muscles by an assessor who had more than 6 years experience in the management of muscle TrPs. TrP diagnosis was performed following the criteria described by Simons et al[13] and Gerwin et al[23]: (1) presence of a palpable taut band in a skeletal muscle, (2) presence of a hyperirritable tender spot in the taut band, (3) local twitch response elicited by snapping palpation of the taut band, and (4) presence of distant referred pain distant in response to TrP compression. These criteria, when applied by an experience assessor, have obtained a good interexaminer reliability (κ) ranging from 0.84 to 0.88.[23]

TrPs were considered active when both the local and the referred pain evoked by digital compression reproduced any pain symptom and the patient recognized the pain as familiar.[13] TrPs were considered latent when the local and referred pain elicited by digital compression did not reproduce any pain symptom recognized by the patient.[13] After TrP palpation on each muscle, participants were asked: "When I pressed this muscle, did you feel any pain locally and in other distant area (referred pain). Please tell me whether the pain that you felt during digital compression reproduced any clinical pain symptom that you suffered from."

PPT

PPT is defined as the minimal amount of pressure where a sensation of pressure first changes to pain.[24] An electronic algometer (Somedic AB, Farsta, Sweden) was used to measure PPT levels (kPa). The pressure was applied at an approximate rate of 30 kPa/s by a 1 cm^2 probe. Participants were instructed to press the switch when the sensation first changed from pressure to pain. The mean of 3 trials (intraexaminer reliability) was calculated and used for the main analysis. A 30 seconds resting period was allowed between each trial. The reliability of pressure algometry has been found to be high the same day [intraclass correlation coefficient = 0.91 (95% confidence interval {CI} 0.82-0.97)],[25] and between 4 separate days (intra-class correlation coefficient = 0.94-0.97).[26]

Study Protocol

The study protocol was the same for patients and controls. An 11-point Numerical Point Rate Scale[27] (0 = no pain, 10 = maximum pain) was used to assess the intensity of spontaneous neck pain and shoulder/axillary pain. Patients were asked to draw the distribution of their pain symptoms on an anatomical body map. Participants were asked to avoid any analgesic or muscle relaxant 24 hours before the examination.

PPTs were first bilaterally assessed over the C5-C6 zygapophyseal joint, deltoid muscle, second metacarpal, and tibialis anterior muscle. The order of point assessment was randomized between participants.

Myofascial TrPs in the upper trapezius, sternocleidomastoid, levator scapulae, suboccipital, scalene, infraspinatus, and pectoralis major muscles were explored. The order of evaluation was also randomized between participants. Both explorations were carried out by the same assessor who was not blinded to the participants' condition as the nature of mastectomy surgery did not permit blinding of the assessor.

Sample Size Determination

The sample size determination and power calculations were performed with software (Tamaño de la Muestra1.1, Spain). The calculations were based on detecting, at least, significant clinical differences of 20% on PPT levels between both the groups[28] with an α-level of 0.05, and a desired power of 80%, an estimated interindividual coefficient of variation for PPT measures of 20%. This generated a sample size of at least 16 participants per group.

PPT Data Management

In this study the magnitude of sensitization was investigated assessing the differences of absolute and relative PPT values between the groups. For relative values we calculated a "PPT index" dividing PPT of each patient at each point by the mean of PPT score of the control group at the same point. A greater PPT index (%) indicates lower degree of sensitization.

Statistical Analysis

Data were analyzed with the SPSS statistical package (16.0 Version). Results are expressed as mean, SD, or 95% CI). The Kolmogorov-Smirnov test was used to analyze the normal distribution of the variables ($P > 0.05$). Quantitative data without a normal distribution (pain intensity, total number of muscle TrP, and number of latent or active TrPs) were analyzed with nonparametric tests and those data with normal distribution (PPT) were analyzed with parametric tests. Differences in the number of TrPs (total, active, or latent TrPs) between groups were assessed with the nonparametric Mann-Whitney U test. The χ^2 test was used to analyze the differences in the size of the distribution of muscle TrPs (active or latent) for each muscle within both the groups. A 2-way analysis of variance (ANOVA) test was used to investigate the differences in PPT assessed over each point (C5-C6 zygapophyseal joint, middle deltoid muscle, second metacarpal, and tibialis anterior) with side (affected/nonaffected in patients or dominant/nondominant in controls) as within-patient factor and group (postmastectomy or controls) as the between-patient factor. A 2-way ANOVA test was also used for assessing differences in PPT indices with side (affected or nonaffected) as within-patient factor and point (C5-C6 zygapophyseal joint, middle deltoid muscle, second metacarpal, and tibialis anterior muscle) as between-patient factor. The Bonferroni test was used as post-hoc analysis in all multiple comparisons.

The nonparametric Kruskal-Wallis test was used to analyze the differences within pain intensity between patients with non-TrPs, latent TrPs, or active TrPs in each analyzed muscle. A 1-way ANOVA test was used to analyze the differences in PPT between patients with non-TrPs, latent TrPs, or active TrPs within each analyzed muscle. The Spearman's rho (r_s) test was used to analyze the association between the number of TrPs (total, active, latent) with neck or shoulder pain intensity and with PPT levels. Finally the r_s was also used to investigate the associated between neck/shoulder pain intensity and PPT over each point. The statistical analysis was conducted at 95% confidence level and a P value < 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Data

Twenty-nine women, aged 32 to 65 years (mean ± SD: 50 ± 8 y) who have received mastectomy surgery after breast cancer, and 23 matched controls, aged 32 to 64 years (mean ± SD: 50 ± 9 y), participated ($P = 0.745$). Fourteen (48%) of the patients had the right side affected whereas the remaining 15 (52%) has the left side affected. Six (22%) patients had breast cancer grade I, 19 (66%) had grade II, and the remaining 3 (12%) grade IIIA. Nineteen (66%) patients received a quadrantectomy, whereas the remaining 10 (34%) received a total mastectomy. All patients underwent axillary lymph node dissection during the operative procedure and had received both radiotherapy plus chemotherapy treatment after the surgical intervention. The mean time from surgery was 10 ± 2 months.

Twenty-five (86%) patients reported spontaneous neck pain (intensity, mean: 6.4; 95% CI 5.3-7.6) whereas 20 (69%) patients showed spontaneous shoulder/axillary pain (intensity, mean: 4.8 95% CI 3.3-6.2). Patients described their pain as burning (n = 27, 93%), electric shock-like (n = 25, 86%), or stabbing (n = 22, 76%). A significant positive correlation ($r_s = 0.564$, $P < 0.001$) between neck pain and shoulder/axillary pain intensity was found. No patients had received tricyclic antidepressants at the time of the study. One patient was taking opioids for pain but it was stopped at least 8 days before the beginning of the study. Five patients (17%) were taking ibuprofen whereas 3 (10%) patients were taking lexatin 500 mg for sleep.

Muscle TrPs

The mean ± SD number of TrPs for each woman with postmastectomy pain was 5.7 ± 2 of which 5.4 ± 1.8 were active TrPs and the remaining 0.4 ± 0.6 were latent TrPs. Healthy controls only had latent TrPs (mean ± SD: 0.5 ± 0.6). The number of TrP between both the groups was significantly different for active TrPs ($z = -6.455$, $P < 0.001$) but not latent TrPs ($z = -1.522$, $P = 0.128$): patients with postmastectomy pain showed a greater number of TrPs than controls.

In all the examined muscles, there was significantly more active muscle TrP in patients with postmastectomy pain compared with healthy controls ($P < 0.001$). Further, the distribution of TrPs between patients and healthy controls was significantly different for both the upper trapezius (affected: $\chi^2 = 24.538$, $P < 0.001$; nonaffected: $\chi^2 = 8.632$, $P = 0.003$), affected sternocleidomastoid ($\chi^2 = 8.654$, $P = 0.013$), suboccipital ($\chi^2 = 23.230$, $P < 0.001$), both the levator scapulae (affected: $\chi^2 = 18.330$, $P < 0.001$;

TABLE 1. Distribution of Muscle TrPs in Patients With Postmastectomy Pain and Healthy Controls

	Patients With Postmastectomy Pain					
	Upper Trapezius Muscle		Sternocleidomastoid Muscle		Levator Scapulae Muscle	
	Affected Side	Nonaffected Side	Affected Side	Nonaffected Side	Affected Side	Nonaffected Side
Active TrPs (n)	19	9	9	3	15	6
Latent TrPs (n)	0	0	2	2	1	0
No TrPs (n)	10	20	18	24	13	23
	Scalene muscle		Pectoralis major muscle		Infraspinatus muscle	
	Affected Side	Nonaffected Side	Affected Side	Nonaffected Side	Affected Side	Nonaffected Side
Active TrPs (n)	17	9	27	0	23	1
Latent TrPs (n)	0	1	0	0	1	2
No TrPs (n)	12	19	2	29	5	26
	Healthy control participants					
	Upper trapezius muscle		Sternocleidomastoid muscle		Levator Scapulae muscle	
	Left side	Right side	Left side	Right side	Left side	Right side
Latent TrPs (n)	0	2	0	2	1	0
No TrPs (n)	23	21	23	21	22	23
	Scalene muscle		Pectoralis major muscle		Infraspinatus muscle	
	Left side	Right side	Left side	Right side	Left side	Right side
Latent TrPs (n)	1	2	0	0	1	4
No TrPs (n)	22	21	23	23	22	19

TrPs indicates trigger points.

nonaffected: $\chi^2 = 6.415$, $P = 0.04$), both the scalene (affected: $\chi^2 = 21.042$, $P < 0.001$; nonaffected: $\chi^2 = 8.642$, $P = 0.013$), affected pectoralis major ($\chi^2 = 44.541$, $P < 0.001$), and affected infraspinatus ($\chi^2 = 32.710$, $P < 0.001$) muscles. Active TrPs within the pectoralis major (n = 27, 93%), infraspinatus (n = 23, 79%), and upper trapezius (n = 19, 65%) muscles were the most prevalent in the affected side within the postmastectomy group. Table 1 summarizes the distribution of muscle TrPs for all muscles in both patients and healthy controls.

The overall spontaneous pain area in this postmastectomy pain group and the local and referred pain pattern from active TrPs are illustrated in Figure 1. Referred pain from latent TrPs, which does not reproduce spontaneous pain, is not illustrated. The combination of the referred pain patterns from active TrPs fully reproduced the overall spontaneous clinical pain pattern in patients with postmastectomy pain.

PPTs

The ANOVA revealed significant differences between both the groups, but not between sides, for PPT levels over the C5-C6 zygapophyseal joint (group: $F = 295.9$, $P < 0.001$; side: $F = 1.182$, $P = 0.28$), deltoid muscle (group: $F = 259.7$, $P < 0.001$; side: $F = 0.108$, $P = 0.74$), second metacarpal (group: $F = 357.6$, $P < 0.001$; side: $F = 1.268$, $P = 0.263$), and tibialis anterior muscle (group: $F = 468.6$, $P < 0.001$; side: $F = 0.165$, $P = 0.685$). Over each point, patients showed bilateral lower PPT levels than healthy controls ($P < 0.001$). Further, a significant interaction between group and side ($F = 6.742$, $P = 0.011$) for PPT levels over the deltoid muscle was also found. Post-hoc analysis revealed that PPTs over the affected deltoid muscle were significantly lower as compared with the nonaffected side (Bonferroni; $P < 0.01$). Table 2 summarizes PPT levels assessed over the C5-C6 zygapophyseal, deltoid muscle, second metacarpal, and tibialis anterior muscle for both sides within each study group.

The ANOVA revealed significant differences for PPT indices between sides ($F = 6.225$, $P = 0.013$), but not between points ($F = 1.1473$, $P = 0.222$). No significant side × points interaction ($F = 1.333$, $P = 0.265$) was found. Post-hoc analysis revealed that PPT index within the affected deltoid muscle was more impaired as compared with PPT index within the affected side ($P < 0.01$, Fig. 2). Finally, there were no significant association between the neck or shoulder/axillary pain intensity and PPT levels was found in any point ($P > 0.2$).

TrP Activity, Pain Intensity, and PPT Levels

Within the postmastectomy pain group, significant positive correlations between the number of active muscle TrPs with neck pain intensity ($r_s = 0.392$, $P = 0.036$) and with shoulder/axillary pain intensity ($r_s = 0.437$, $P = 0.018$) were found: the greater the number of active TrPs, the greater the intensity of neck and shoulder/axillary pain. No significant association between the number of TrPs and PPT levels over any point was found ($P > 0.4$).

Further, the Kruskal-Wallis test revealed that patients with active TrPs in the upper trapezius muscle showed greater intensity of neck ($P = 0.006$) and shoulder/axillary pain ($P < 0.05$) than those patients with no TrPs in the same muscle. In addition, intensity of neck pain was related to the presence of active TrPs within the affected sternocleidomastoid muscle (P = 0.049). Finally, active TrPs in the affected pectoralis muscle were also related to a greater intensity of neck ($P = 0.03$) and shoulder/axillary ($P = 0.045$) pain. Patients with active TrPs in these muscles showed greater pain intensity than those without TrPs in the same muscles. Table 3 summarizes neck and shoulder/axillary pain depending on TrP activity on each examined muscle within the affected side, whereas Table 4 shows the same results for muscles located within the nonaffected side.

Finally, PPT levels were also found to be related to active TrPs in some muscles: (1) PPTs over the affected

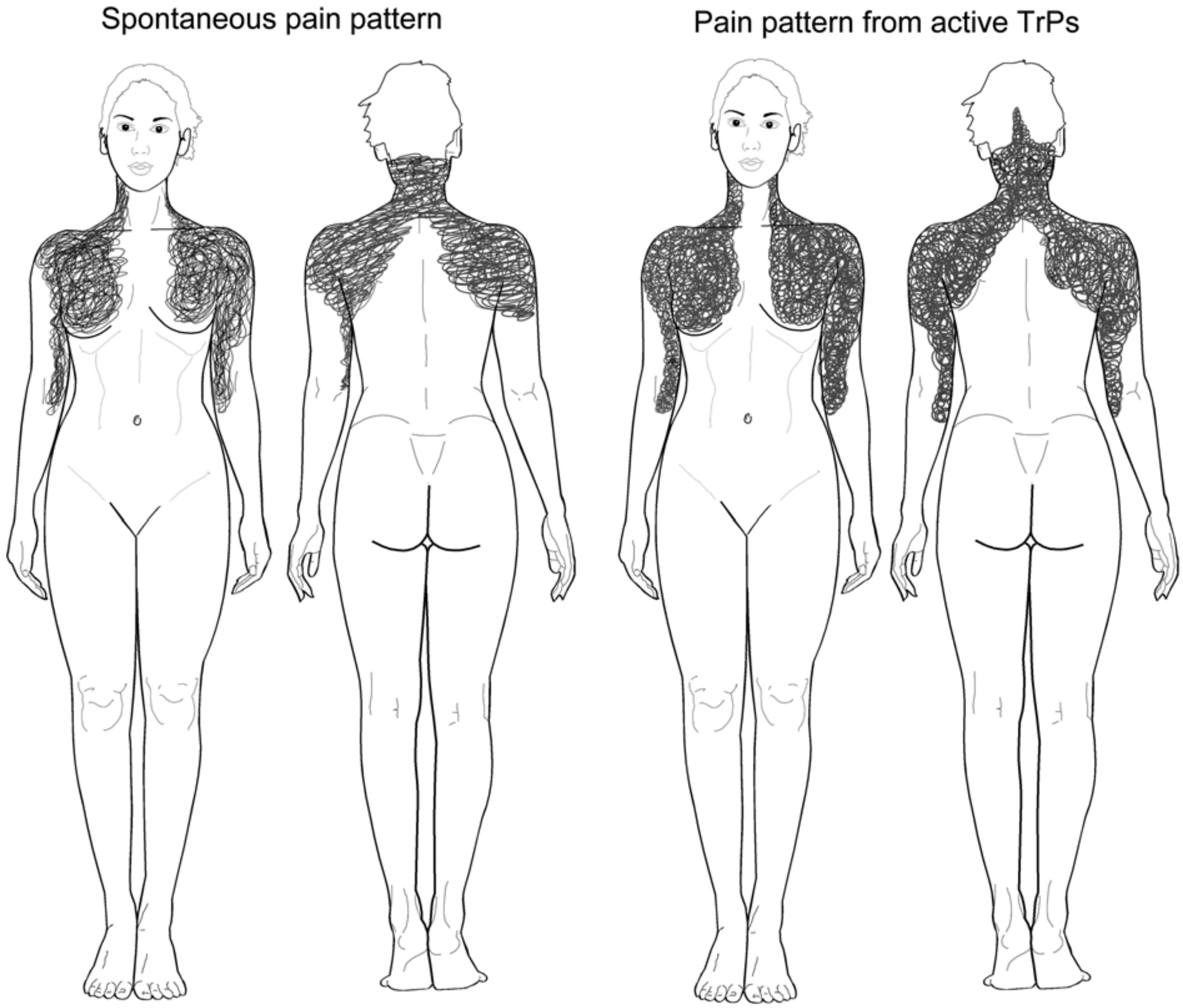

FIGURE 1. Overall spontaneous pain pattern in patients with postmastectomy pain (left) and the induced-pain pattern from active TrPs (right). Note that the combination of the referred pain patterns from active TrPs fully reproduced the overall spontaneous clinical pain pattern in patients with postmastectomy pain. TrPs indicates trigger points.

deltoid muscle were significantly lower ($t = 2.097$; $P = 0.045$) in patients with active TrPs in the suboccipital muscles (mean ± SD: 113.4 ± 50.6 kPa) as compared with those patients with no suboccipital muscle TrPs (mean ± SD: 154.6 ± 51.8 kPa), (2) PPTs over affected and unaffected tibialis anterior muscles were significantly lower (both, $t = 2.151$, $P = 0.041$) in patients with active TrPs in the levator scapulae muscle (mean ± SD: 224.1 ± 75.1 kPa, 230.2 ± 70.2 kPa, respectively) as compared with those patients with no levator scapulae TrPs (mean ± SD: 277.5 ± 78.5 kPa, 282.8 ± 57.2 kPa, respectively), (3) PPT levels over the affected deltoid muscle were lower ($t = 2.001$, $P = 0.048$) in patients with active TrPs in the infraspinatus muscle (mean ± SD: 136.9 ± 55.5 kPa) as compared with those patients with no infraspinatus TrPs (mean ± SD: 155.2 ± 56.3 kPa).

TABLE 2. Pressure Pain Thresholds (kPa) in Patients With Postmastectomy Pain and Healthy Controls

	C5-C6 Zygapophyseal Joint*	Deltoid Muscle*	Second Metacarpal*	Tibialis Anterior*
Patients with postmastectomy pain				
Affected	121.4 ± 43.8 (103.5-139.2)	138.9 ± 54.4 (122.1-155.8)	149.1 ± 42.6 (130.8-167.5)	247.8 ± 78.8 (222.5-273.2)
Nonaffected	127.6 ± 42.8 (109.7-144.4)	165.3 ± 40.7 (148.5-182.1)	170.8 ± 52.9 (152.5-189.2)	253.4 ± 67.7 (228.1-278.8)
Healthy control participants				
Dominant	281.8 ± 29.7 (261.8-301.9)	375.5 ± 48.1 (356.6-394.3)	345.8 ± 57.5 (325.2-366.4)	552.9 ± 59.5 (524.4-581.3)
Nondominant	296.4 ± 70.8 (276.4-316.5)	355.1 ± 35.7 (336.2-373.9)	346.3 ± 46.0 (325.6-366.9)	536.2 ± 64.9 (507.7-564.6)

Values ± SD are expressed as mean (95% confidence interval).
*Significant differences between patients and controls (2-way analysis of variance test).

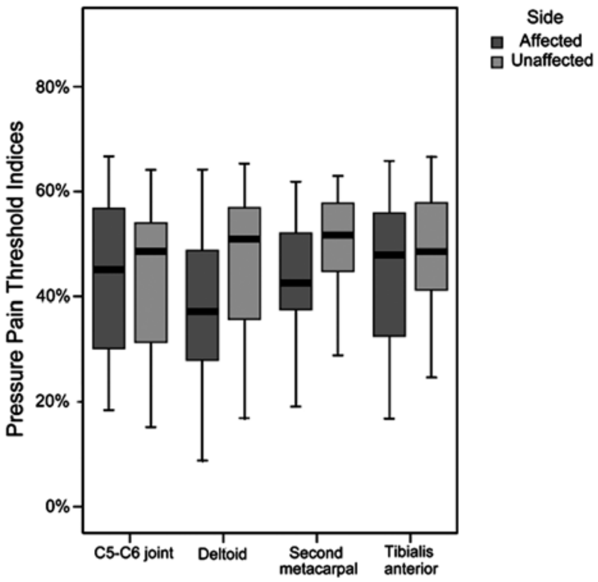

FIGURE 2. Pressure pain threshold indices in C5-C6 zygapophyseal joint, deltoid muscle, second metacarpal, and tibialis anterior muscle. The boxes represent the mean and percentile scores and the error bars represent the SD.

DISCUSSION

The results of this study showed the existence of multiple active muscle TrPs in neck and shoulder musculature and widespread muscle pressure pain hyperalgesia in patients with postmastectomy pain. The induced local and referred pain pattern from active TrPs reproduced neck and shoulder/axillary complaints and pain patterns in patients with postmastectomy pain. In contrast, no active TrPs, but only latent TrPs, were found in healthy controls. A greater number of active TrPs were related to greater intensity of pain: the greater the pain intensity, the greater the number of TrPs. Finally, PPT levels over some muscles were lower in patients with active TrPs as compared with those patients without TrPs in the same muscles. Our results suggest both peripheral and central sensitization mechanisms in patients with postmastectomy pain.

Local and Referred Pain From Active Muscle TrPs in Postmastectomy Pain

Active TrPs within the upper trapezius, sternocleidomastoid, suboccipital, levator scapulae, scalene, infraspinatus, and pectoralis major muscles were found in patients with postmastectomy pain, but not in healthy controls. Indeed, the induced local and referred pain pattern from active TrPs in these muscles reproduced the spontaneous neck and shoulder/axillary pain within the postmastectomy pain group. When active TrPs were explored, patients spontaneously reported: “Yes, this is exactly the pain that I usually feel in the neck and the shoulder/axillary regions.” These results support that the local and referred pain from active TrPs in neck and shoulder muscles are associated with postmastectomy pain.

Active TrPs were not found in healthy controls as they did not have clinical pain symptomatology. Only a small number of latent TrPs was found within the control group that was similar to the number of latent muscle TrPs found in the postmastectomy pain group. These results further support the relevance of active, but not latent, muscle TrPs for postmastectomy pain. It has been proposed that latent TrPs may become active under the influence of several factors such as muscle trauma, surgery, or sustained activities.[29] The fact that TrPs found within the postmastectomy pain group were active may be related to activation of TrPs after surgery. Activation of TrPs within the

TABLE 3. Intensity of Neck and Shoulder/Axillary Pain Depending on the Presence of Myofascial Trigger Points (TrPs) in Each Muscle Within the Affected Side in Patients With Postmastectomy Pain

	Neck Pain Intensity (NPRS)	Shoulder/Axillary Pain Intensity (NPRS)
Upper trapezius muscle		
Active TrPs (n = 19)	7.5 ± 0.5*	5.7 ± 0.8*
No TrPs (n = 10)	4.4 ± 1.1	3.9 ± 1.3
Sternocleidomastoid muscle		
Active TrPs (n = 9)	7.7 ± 0.5*	5.8 ± 1.1
No TrPs (n = 18)	5.7 ± 0.8	4.1 ± 0.9
Levator scapulae muscle		
Active TrPs (n = 15)	6.6 ± 0.8	5.3 ± 0.9
No TrPs (n = 13)	6.1 ± 0.9	3.9 ± 1.1
Suboccipital muscles		
Active TrPs (n = 18)	6.7 ± 0.8	4.3 ± 0.9
No TrPs (n = 11)	6.2 ± 0.7	5.5 ± 1.1
Scalene Muscle		
Active TrPs (n = 17)	6.9 ± 0.6	5.3 ± 0.9
No TrPs (n = 12)	5.6 ± 1.1	3.9 ± 1.2
Pectoralis major muscle		
Active TrPs (n = 27)	6.7 ± 0.5*	5.1 ± 0.7*
No TrPs (n = 2)	2.0 ± 2.0	0.0 ± 0.0
Infraspinatus muscle		
Active TrPs (n = 23)	6.2 ± 0.6	4.2 ± 0.8
No TrPs (n = 5)	7.4 ± 0.8	6.2 ± 1.6

Values are expressed as means ± standard error.
*Significantly different between active TrP subgroup and non-TrP subgroup (Kruskal-Wallis test, $P < 0.05$).
NPRS indicates Numerical Pain Rate Scale (0-10).

TABLE 4. Intensity of Neck and Shoulder/Axillary Pain Depending on the Presence of Myofascial TrPs in Each Muscle Within the Unaffected Side in Patients With Postmastectomy Pain

	Neck Pain Intensity (NPRS)	Shoulder/Axillary Pain Intensity (NPRS)
Upper trapezius muscle		
Active TrPs (n = 9)	7.4 ± 0.5	6.3 ± 1.1*
No TrPs (n = 20)	6.0 ± 0.8	4.0 ± 0.9
Sternocleidomastoid muscle		
Active TrPs (n = 0)	8.7 ± 0.7	8.3 ± 0.3
No TrPs (n = 4)	6.0 ± 0.6	4.2 ± 0.8
Levator scapulae muscle		
Active TrPs (n = 6)	6.7 ± 1.4	5.5 ± 1.3
No TrPs (n = 23)	6.3 ± 0.6	4.6 ± 0.8
Scalene muscle		
Active TrPs (n = 9)	6.3 ± 0.9	6.4 ± 1.0
No TrPs (n = 19)	6.4 ± 0.7	3.8 ± 0.9
Pectoralis major muscle		
Active TrPs (n = 0)	—	—
No TrPs (n = 29)	—	—
Infraspinatus muscle		
Active TrPs (n = 1)	—	—
No TrPs (n = 26)	6.3 ± 0.6	4.3 ± 0.7

Values are expressed as mean ± standard error.
*Significantly different between active TrP subgroup and non-TrP subgroup (Kruskal-Wallis test, $P < 0.05$).
NPRS indicates Numerical Pain Rate Scale (0-10); TrPs, trigger points.

pectoralis major muscle after axillary surgery has been previously described in a case report.[19] In this study, active TrPs in the pectoralis major muscle of the operated side were found in 93% of the patients with postmastectomy pain. These findings support the role of the pectoralis major muscle in this patient population. As the pectoralis major muscle is anatomically located over the breast, it is possible that it would be the most affected muscle by the surgical procedure. Undoubtedly, active TrPs in other muscles, like infraspinatus (79%) and upper trapezius (65%), were also highly prevalent in our sample of patients with postmastectomy pain. In fact, our women with postmastectomy pain showed bilateral pain patterns although no active TrPs were found in the pectoralis major muscle on the unaffected side. This finding may be related to the presence of TrPs in other muscles different from the pectoralis major, for example scalene, upper trapezius, within the unaffected side.

An interesting finding was that the number of TrPs was related to a greater pain intensity of neck and shoulder/axillary symptoms. Further the presence of active TrPs in the upper trapezius and pectoralis major muscles was related to a greater intensity of neck and shoulder/axillary pain. These findings further support the role of active TrPs in postmastectomy pain. In fact, a greater number of muscle TrPs suggests the presence of spatial summation of TrP activity in postmastectomy-related pain. However, we do not know if the presence of multiple active TrPs is from cancer pain, surgical procedure, or postsurgery factors, such as tissue scars. Undoubtedly, other pain generators, like nerve injuries, would be also involved.

Finally, multiple active TrPs in the same muscle have been previously described in shoulder pain,[30] chronic tension type headache,[31] and fibromyalgia syndrome.[32] This study is the first to report the presence of TrPs in multiple and different muscles in patients with postmastectomy pain. Nevertheless, it may be possible that the muscles examined in this study also showed multiple active TrPs at the same time. Future studies investigating the presence of multiple active TrPs in the same muscle in patients with postmastectomy pain are needed.

Sensitization Mechanisms Associated to Postmastectomy Pain

In this study, bilaterally and widespread pressure hypersensitivity was found in patients with postmastectomy pain reflected as PPT levels significantly decreased over the C5-C6 zygapophyseal joint, middle deltoid muscle, second metacarpal, and tibialis anterior muscle. These findings suggest multisegmental central sensory sensitization in patients with postmastectomy pain. This hypothesis is also supported by the fact that the magnitude of PPT changes was similar in the C5-C6 zygapophyseal joint (43%), the deltoid muscle (37% to 46%), the second metacarpal (43% to 49%), and the tibialis anterior muscle (44% to 47%), suggesting a widespread increased responsiveness to pressure pain in patients with postmastectomy pain. Further, PPT changes within the affected deltoid muscle were greater than the remaining points, suggesting a greater sensitization in the surgical area.

Our findings supporting a central sensitization in women with postmastectomy pain agree with the results reported by a previous study that found increased evoked pain intensity after repetitive pinprick stimulation in the vicinity of a breast scar in women with pain after breast cancer surgery.[21] This study showed that patients with postmastectomy pain and abnormal sensitivity showed central sensitization,[21] whereas the present study found that central sensitization is present in a different cohort of patients with postmastectomy pain. The hypothesis of the hyperexcitability of the central nervous system in postmastectomy pain is clinically supported by the fact that many breast cancer patients suffer from widespread diffuse persistent pain.[33]

The existence of generalized sensitization in local pain syndromes, such as low back pain,[34] migraine,[35] repetitive strain injury,[36] lateral epicondylalgia,[37] tension type headache,[38] knee osteoarthritis,[39] or carpal tunnel syndrome,[40] suggests that sustained peripheral noxious inputs to the central nervous system play a role in the initiation and maintenance of central sensitization processes.[41] Gottrup et al[21] suggested that peripheral sensitization contributes to clinical pain and sensory disturbances in patients with postmastectomy owing to nociception from damaged small nerve fibers during the operative procedure. In fact, postmastectomy pain is considered to be neuropathic in origin, as abnormal temporal pain summation shown by these patients is similar to that reported in patients with nerve injury pain.[42–44] Nevertheless, sensory changes found in postmastectomy pain patients suggest that different peripheral receptors or different central mechanisms may be involved at the same time.

Our results also reflect the presence of peripheral muscle sensitization in patients with postmastectomy pain as active TrPs suggest irritation of muscle nociceptors. It is known that active muscle TrPs constitute a source of nociception as high levels of algogenic substances[14,15] were found in active TrPs. In addition, a recent study has demonstrated the existence of both nociceptive and nonnociceptive hypersensitivity at muscle TrP.[45] It is possible that muscle pain would also be involved in postmastectomy pain in conjunction with nerve injury. In fact, we found that lower PPTs were negatively related to the presence of active TrPs in some muscles, which indicates that active muscle TrPs spatially increase the mechanical pain sensitivity peripherally and centrally, as PPT were not measured directly on the TrP, but on fixed points. It is important to note that we found 5 active TrPs within each patient with postmastectomy pain, supporting the assumption of spatial summation of TrP activity in these patients. As active TrPs constitute a peripheral sensitization focus, the presence of multiple active TrPs can exert a spatial summation of nociceptive barrage to the dorsal horn neurons. Longitudinal studies are needed to elucidate the role of active TrPs to the development of postmastectomy pain.

Clinical Implications

This study has several clinical implications. First, the findings suggest that postmastectomy pain also has a muscle pain component that should be treated to relieve symptoms. It is possible that inclusion of muscle TrP inactivation into physical therapy programs[46,47] may be beneficial to reduce pain and to prevent joint restriction in postmastectomy pain. In addition, it is possible that inactivation of TrPs could change the sensitization found in this study in these patients, although additional studies are needed. Finally, several drugs for the management of central sensitization should be advocated for postmastectomy pain.

CONCLUSIONS

This study showed the existence of multiple active muscle TrPs in neck and shoulder musculature and widespread pressure pain muscle hyperalgesia in patients with postmastectomy pain. The induced local and referred pain patterns from active TrPs reproduced neck and shoulder/axillary symptoms in postmastectomy pain. Our results suggest both peripheral and central sensitization mechanisms in patients with postmastectomy pain.

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PAPER II

Widespread Mechanical Pain Hypersensitivity as a Sign of Central Sensitization after Breast Cancer Surgery: Comparison between Mastectomy and Lumpectomy

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Pain Med

Journal Citation Reports Area
Medicine, General & Internal: 30/153 Q1

2011 Jan;12(1):72-8

Pain Medicine

Pain Medicine 2011; 12: 72–78
Wiley Periodicals, Inc.

PALLIATIVE CARE SECTION

Original Research Article

Widespread Mechanical Pain Hypersensitivity as a Sign of Central Sensitization after Breast Cancer Surgery: Comparison between Mastectomy and Lumpectomy

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Conflict of interest/Competing interests: None to declare.

Abstract

Objective. **To investigate the differences in widespread pressure pain hypersensitivity after two surgery approaches for breast cancer: mastectomy or lumpectomy.**

Design. **A cross-sectional blinded study.**

Setting. **Widespread pressure pain hypersensitivity has been suggested as a sign of central sensitization. No study has previously investigated the presence of widespread pain pressure hypersensitivity after breast cancer surgery.**

Patients. **Twenty-one women (age: 52 ± 9 years old) who had received lumpectomy after breast cancer, 21 women (mean age: 50 ± 10 years old) who had received mastectomy surgery after breast cancer, and 21 healthy women (age: 51 ± 10 years old) participated.**

Outcome Measures. **Pressure pain thresholds (PPT) were bilaterally assessed over C5-C6 zygapophyseal joint, deltoid muscle, second metacarpal, and the tibialis anterior muscle.**

Results. **Women with mastectomy had greater intensity of neck ($t = -2.897$; $P = 0.006$) and shoulder/axillary ($t = -2.609$; $P = 0.013$) pain as compared with those who received lumpectomy. The results showed that PPT were significantly decreased bilaterally over the C5-C6 zygapophyseal joint, deltoid muscle, second metacarpal, and tibialis anterior muscle in both lumpectomy and mastectomy groups as compared with healthy women in all points ($P < 0.001$), without differences between both breast cancer groups ($P = 0.954$). No significant differences in the magnitude of PPT levels between both breast cancer groups were found (all, $P > 0.450$). PPT levels over some areas were negatively associated with the intensity of pain in the mastectomy, but not lumpectomy, group.**

Conclusion. **The current study found widespread pressure pain hyperalgesia in women who received breast cancer surgery suggesting central spreading**

sensitization. The degree of central sensitization was similar between lumpectomy and mastectomy surgery.

Key Words. Mastectomy; Lumpectomy; Pressure Pain; Sensitization

Introduction

Breast cancer is the most common form of cancer among women [1]. A recent study found that since 1980, the breast cancer incidence rate has increased by 2.9% per year in Spain [2]. In the United States, the National Cancer Institute has estimated that 1.09% (95% confidence interval [CI] 0.95–1.24%) of women aged 30 to 84 years had a lifetime absolute breast cancer risk of ≥20% which translates to 880,063 U.S. women [3]. Screening programs and advances in therapeutic and diagnostic approaches have raised survivor rate in last years close to 70% at 5 years of diagnosis [4]. There has been an increasing interest for improving surgical treatments for breast cancer, with two current different surgical options: mastectomy (whole breast removed) or lumpectomy (tumor and surrounding tissue removed). In fact, lumpectomy surgery is preferred in younger patients with smaller breasts, as it is less cosmetically mutilating [5]. Additionally, the incidence of postoperative complications has been found to be higher with mastectomy (35%) than with lumpectomy (24%) procedures [6].

Pain is the most frequent impairment after breast cancer treatment (20–65%) [7,8] with a strong relationship to higher self-perceived disability and lower quality of life [9]. In addition, preoperative pre-incisional paravertebral block seems to reduce the prevalence of chronic pain after breast cancer surgery [10]. The presence of persistent pain beyond the period of "normal" healing after breast cancer surgery is called "postmastectomy pain" and it is attributed to the damage of peripheral nerves during the operative procedure [11]. Nevertheless, there is an increasing evidence suggesting that postmastectomy pain may be also related to changes in nociceptive pain gain. Indeed, Andrykowski et al. found that mastectomy may enhance the experience of pain at distant sites via alterations in neuro-endocrine profiles or by sensitizing the central nervous system [12]. Gottrup et al. found in 15 women with postmastectomy pain and abnormal sensitivity that ongoing C-fiber inputs can induce a central sensitization state similar to that seen in other pain patient populations [13].

Several quantitative sensory tests are proposed for investigating the presence of sensitization mechanisms in chronic conditions [14]. One of the most common procedures used for evaluating the hyperexcitability of the central nervous system is calculating the pressure pain thresholds (PPT). In fact, several studies have investigated the nociceptive system in different chronic conditions by assessing widespread mechanical pain hypersensitivity, e.g., whiplash [15], fibromyalgia [16], repetitive strain injury [17], tension type headache [18], low back pain [19], lateral epicondylalgia [20], carpal tunnel syndrome [21], or knee osteoarthritis [22]. These studies found widespread pressure pain hypersensitivity as a sign of central sensitization in these chronic pain conditions. Nevertheless, to the best of the authors' knowledge, there are no previous studies investigating the presence of widespread pressure hypersensitivity after breast cancer surgery. Therefore, the aim of this study was to investigate the differences in the presence of widespread pressure pain hypersensitivity after two approaches for breast cancer: mastectomy or lumpectomy. We hypothesized that women receiving a total removal of the breast (mastectomy) would have greater widespread pressure pain hypersensitivity than those receiving a partial removal of the breast (lumpectomy).

Materials and Methods

Participants

Patients were recruited from the Department of Breast Oncology at the University Hospital Virgen de las Nieves, Granada, Spain. To be eligible for the study, participants had to meet the following criteria: 1) first time with a primary diagnosis of breast cancer (grades I–IIIA); 2) women who had received a simple mastectomy with breast reconstruction or women who had received lumpectomy; 3) those who received the surgery for at least 6 months and since surgery without sign recurrence; 4) receiving post-primary adjuvant treatment (radiation, cytotoxic chemotherapy) at least 3 months before the study; and 5) adults at least 18 years of age.

Exclusion criteria were: 1) breast surgery for cosmetic reasons or prophylactic mastectomy; 2) other medical conditions (i.e., arthritis); 3) presence of lymphoedema; 4) recurrent cancer; or 5) previous diagnosis of fibromyalgia syndrome [23].

Additionally, age-matched right-handed controls were recruited from volunteers who responded to a local announcement and were excluded if they exhibited a history of neck, shoulder or arm pain, history of trauma, or diagnosis of any systemic disease. The study protocol was approved by the local Ethics Committee (FIS 08-ETES-PI0890418) and conducted following the Helsinki Declaration. All participants signed an informed consent prior to their inclusion.

PPT

4Pressure pain threshold is defined as the minimal amount of pressure where a sensation of pressure first changes to pain [24]. An electronic algometer (Somedic AB, Farsta, Sweden) was used to measure PPT levels (kilopascal [kPa]). The pressure was applied at approximately rate of 30 kPa/second by a 1 cm^2 probe. Participants were instructed to press the switch when the sensation first changed from pressure to pain. The mean of three trials (intraexaminer reliability) was calculated and used for the main analysis. A 30-second resting period was allowed between each trial. The reliability of pressure algometry has been found to be high the same day (intraclass correlation coefficient [ICC] = 0.91 [95% CI 0.82–0.97]) [25,26].

Sample Size Determination

The sample size determination and power calculations were performed with appropriate software (Tamaño de la Muestra1.1©, Madrid, Spain). The calculations were based on detecting, at least, significant clinically differences of 20% on PPT levels between both breast cancer groups [27] with an alpha level of 0.05, and a desired power of 80% and an estimated interindividual coefficient of variation for PPT measures of 20%. This generated a sample size of at least 16 participants per group.

Study Protocol

The study protocol was the same for both group of patients and controls. An 11-point numerical point rate scale [28] (0 = no pain; 10 = maximum pain) was used to assess the intensity of spontaneous neck pain and shoulder/axillary pain. Patients were asked to draw the distribution of their pain symptoms on an anatomical body map. Participants were asked to avoid any analgesic or muscle relaxant 24 hours prior to the examination. PPT levels were bilaterally assessed over the C5-C6 zygapophyseal joint, the deltoid muscle, the second metacarpal, and the tibialis anterior muscle. The order of point assessment was randomized between participants.

Pressure pain threshold exploration was done by an assessor who was blinded to the participants' condition. Due to the nature of breast cancer surgery and in order to satisfactorily blind assessor, PPT examination was performed with subjects lying supine with a sheet over their chest.

PPT Data Management

In the current study, the magnitude of sensitization was investigated assessing the differences of absolute and relative PPT values between both groups. For relative values, we calculated a "PPT index" dividing PPT of each patient at each point by the mean of PPT score of the control group at the same point. A greater PPT index (%) indicates lower degree of sensitization.

Statistical Analysis

Data were analyzed with the SPSS statistical package (16.0 version). Results are expressed as mean, standard deviation (SD), or 95% CI. The Kolmogorov–Smirnov test was used to analyze the normal distribution of the variables ($P > 0.05$). As PPT showed normal distribution, parametric tests were used. A two-way analysis of variance (ANOVA) test was used to investigate the differences in PPT assessed over each point (C5-C6 zygapophyseal cervical joint, deltoid muscle, second metacarpal, and tibialis anterior) with side (affected/non-affected within patients or dominant/non-dominant controls) as within-subject factor and group (mastectomy, lumpectomy, or controls) as between-subject factor. A three-way ANOVA test was used for assessing differences in PPT indices with side (affected or non-affected) and point (C5-C6 zygapophyseal joint, middle deltoid muscle, second metacarpal, and tibialis anterior) as within-patient factors and group (lumpectomy or mastectomy) as between-patient factor. The Bonferroni test was used as post hoc analysis in all the multiple comparisons. Differences in neck and shoulder/axillary pain mean intensity between both patients groups were assessed with the unpaired student *t*-test. The Pearson correlation test (r) was used to investigate the association between neck and shoulder/axillary pain intensity and PPT over each point with each patient group. The statistical analysis was conducted at 95% confidence level. A $P < 0.05$ was considered statistically significant.

Results

Demographic and Clinical Data of the Patients

Twenty-one women, aged 30–70 years old (mean ± SD: 52 ± 9 years) who had received lumpectomy surgery after breast cancer; 21 women, aged 30–69 years old (mean ± SD: 50 ± 10 years) who had received mastectomy surgery after breast cancer; and 21 healthy women, aged 30–69 years old (mean ± SD: 51 ± 10 years) participated ($F = 0.541$; $P = 0.791$).

Within the lumpectomy group, 10 (48%) had the right breast affected whereas the remaining 11 (52%) had the left breast affected. Within the mastectomy group, eight (47%) had the right breast affected and the remaining nine (53%) had the right side ($\chi^2 = 0.973$; $P = 0.615$). Further, in the lumpectomy group, eight (38%) patients had breast cancer grade I, 11 (52%) had grade II and the remaining two (10%) had breast cancer grade IIIA, whereas in the mastectomy group, two (18%) patients had breast cancer grade I, 11 (65%) had grade II, and the remaining three (27%) had cancer grade IIIA ($\chi^2 = 4.428$; $P = 0.219$). All patients underwent axillary lymph node dissection during the operative procedure and received both radiotherapy and chemotherapy treatment after the surgery. The mean time from breast surgery intervention was 11 ± 3 months in the lumpectomy group and 14 ± 6 months within the mastectomy group ($t = -1.725$; $P = 0.125$).

Within the lumpectomy group, 13 (62%) women reported spontaneous neck pain (mean intensity: 4.0 ± 3.5) whereas eight (38%) had shoulder/axillary pain (mean intensity: 2.4 ± 3.5). Within the mastectomy group, 16 (95%) women reported spontaneous neck pain (mean intensity: 7.1 ± 2.7), whereas 13 (77%) had shoulder/axillary pain (mean intensity: 5.6 ± 3.8). Therefore, women who received mastectomy surgery had greater intensity of neck ($t = -2.897$; $P = 0.006$) and shoulder/axillary ($t = -2.609$; $P = 0.013$) pain than those who had received lumpectomy.

A significant positive correlation ($r_s = 0.469$; $P = 0.032$) between neck pain and shoulder/axillary pain intensity was found within the lumpectomy group, but not in the mastectomy group ($r_s = 0.209$; $P = 0.421$). Eight women (38%) in the lumpectomy group and six women (35%) in the mastectomy group were receiving tamoxifen, whereas eight (38%) women within the lumpectomy group, and seven women (41%) in the mastectomy group were taking aromatase inhibitors ($\chi^2 = 0.096$; $P = 0.953$). Finally, two women (10%) in the lumpectomy group and three (17%) in the mastectomy group were taking trastuzumab ($\chi^2 = 0.543$; $P = 0.640$).

PPT Levels

The ANOVA revealed significant differences between groups, but not between sides, for PPT levels over the C5-C6 zygapophyseal joint (group: $F = 48.456$; $P < 0.001$; side: $F = 0.327$; $P = 0.568$), deltoid muscle (group: $F = 45.024$; $P < 0.001$; side: $F = 1.891$; $P = 0.172$), second metacarpal (group: $F = 39.554$; $P < 0.001$; side: $F = 0.434$; $P = 0.511$), and tibialis anterior muscle (group: $F = 55.838$; $P < 0.001$; side: $F = 1.396$; $P = 0.240$). No significant interaction between group * side was found: C5-C6 zygapophyseal joint ($F = 0.004$; $P = 0.996$), deltoid muscle ($F = 2.038$; $P = 0.135$), second metacarpal ($F = 0.558$; $P = 0.574$), and tibialis anterior muscle ($F = 0.887$; $P = 0.415$). The post hoc analysis revealed that both lumpectomy and mastectomy groups showed bilateral lower PPT than healthy women in all points ($P < 0.001$), without differences between both breast cancer groups (all, $P > 0.952$). Table 1 summarizes PPT levels assessed over the C5-C6 zygapophyseal, deltoid muscle, second metacarpal, and tibialis anterior muscle for both sides within each study group.

Pressure Pain Indices

The three-way ANOVA revealed significant effects for side ($F = 7.237$; $P = 0.008$), but not for groups or points for PPT indices (group: $F = 0.043$; $P = 0.836$; point: $F = 0.819$; $P = 0.484$). Additionally, no significant interactions between group * side ($F = 0.111$; $P = 0.739$), group * point ($F = 0.058$; $P = 0.982$), side * point ($F = 1.308$; $P = 0.272$), or group * side * point ($F = 0.167$; $P = 0.918$) were found (Figure 1).

PPT and Current Level of Pain

Within the lumpectomy group, no significant association between either neck or shoulder/axillary pain intensity and PPTs in any point ($P > 0.347$) was found. On the contrary, in the mastectomy group, neck pain intensity was negatively associated with PPT levels over the affected deltoid ($r_s = -0.619$; $P = 0.008$) and both tibialis anterior (affected: $r_s = -0.511$; $P = 0.036$; non-affected: $r_s = -0.659$; $P = 0.004$) muscles; whereas shoulder/axillary pain intensity was negatively associated with PPT levels over both C5-C6 zygapophyseal joints (affected: $r_s = -0.531$; $P = 0.028$; non-affected: $r_s = -0.587$; $P = 0.013$), over the affected deltoid ($r_s = -0.526$; $P = 0.030$) and the affected tibialis anterior ($r_s = -0.567$; $P = 0.018$) muscle. In summary, the greater the neck or shoulder/axillary intensity, the lower the PPT levels over these points.

Discussion

The main finding of the current study was a bilaterally and widespread pressure pain hypersensitivity in women who had received breast cancer surgery as compared with

Table 1 Pressure pain thresholds (kilopascal) in breast cancer survivors and healthy controls

	C5-C6 Zygapophyseal Joint*	Deltoid Muscle*	Second Metacarpal*	Tibialis Anterior*
Breast cancer treated with lumpectomy				
Affected	171.8 ± 58.0 (146.4–197.4)	198.9 ± 83.2 (164.4–233.3)	224.3 ± 73.8 (194.1–254.5)	304.1 ± 63.4 (257.4–350.9)
Non-affected	177.6 ± 58.2 (152.1–203.1)	237.4 ± 71.2 (203.0–271.9)	224.9 ± 51.4 (194.7–255.2)	351.3 ± 44.4 (304.5–398.1)
Breast cancer treated with mastectomy				
Affected	179.0 ± 65.8 (150.6–207.3)	195.1 ± 51.1 (156.7–232.5)	209.5 ± 97.0 (175.9–243.1)	312.3 ± 60.2 (260.3–364.2)
Non-affected	184.4 ± 61.7 (156.0–212.7)	238.4 ± 62.8 (200.1–276.6)	237.7 ± 87.3 (204.3–271.5)	348.4 ± 43.7 (296.4–400.4)
Healthy control subjects				
Dominant	285.5 ± 28.5 (260.0–310.9)	373.4 ± 48.2 (338.9–407.9)	345.5 ± 59.8 (315.2–375.7)	554.8 ± 60.7 (508.1–601.6)
Non-dominant	293.1 ± 73.4 (267.6–318.6)	352.4 ± 34.5 (317.9–386.8)	342.0 ± 45.3 (311.8–372.2)	542.4 ± 64.4 (495.7–589.2)

* Significant differences between both breast cancer groups and controls (two-way analysis of variance test).
Values are mean ± SD (95% confidence interval for the mean).

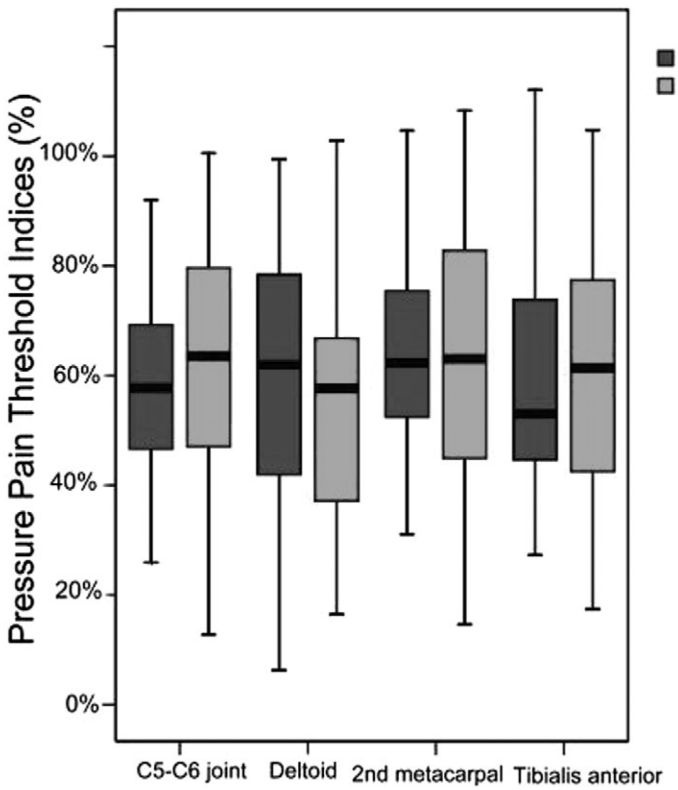

Figure 1 Pressure pain threshold indices. The boxes represent the mean and the 25 and 75 percentile scores and the error bars represent the two standard deviations.

healthy women. In fact, widespread mechanical hypersensitivity was similar in women who received either lumpectomy or mastectomy, suggesting that central sensitization is present independently of the type of breast cancer surgery received. Additionally, PPT levels over some areas were negatively associated with the intensity of pain, suggesting a role of peripheral nociception after breast cancer surgery.

Bilateral and widespread pressure hypersensitivity found in the current study suggests central sensitization in women who had received either type of breast cancer surgery. The fact that lower PPT levels were found in pain-free distant areas, i.e., second metacarpal and tibialis anterior muscle, support the presence of second order neuron (or higher) sensitization mechanisms. In fact, the magnitude of sensitization, represented by pressure pain indices, was similar between symptomatic (C5-C6 zygapophyseal joint: 60–63%; deltoid muscle: 53–67%) and non-symptomatic (second metacarpal: 60–69%); tibialis anterior muscle: 54–69%) areas in both lumpectomy and mastectomy groups. Our findings supporting a central sensitization in women who had received breast cancer surgery agree with the results previously reported for women with postmastectomy pain where increased evoked pain intensity following repetitive pinprick stimulation in the vicinity of a breast scar was found [13]. This study showed that patients with postmastectomy pain and abnormal sensitivity had central sensitization [13]. Our study suggests that central sensitization is also present in women with breast cancer who had received lumpectomy or mastectomy. In fact, the hypothesis of hyperexcitability of the central nervous system after breast cancer surgery is clinically supported by the fact that many patients suffer from widespread diffuse persistent pain after surgery [29].

A relevant finding from the current study is that central sensitization was similar after either surgery, independently of partial (lumpectomy) or total (mastectomy) breast removal. In addition, a greater degree of sensitization in the affected deltoid muscle was found in both breast cancer groups, suggesting a greater sensitization in the surgical area. Gottrup et al. suggested that peripheral sensitization contributes to clinical pain and sensory disturbances in postmastectomy pain due to nociception from damaged small nerve fibers during the operative procedure [13]. One possible reason for our findings is that nerve injury may be similar in both surgical approaches, although this is unlikely as lumpectomy is considered less aggressive than mastectomy. Another reason for similar sensitization in both groups may be because all women received chemotherapy after the surgery which can influence sensitization processes. Chemotherapy can cause peripheral neuropathy and changes in afferent vagal activity leading to widespread changes in pain sensitivity [30]. Therefore, it would be interesting to compare the degree of sensitization with a control group that received similar chemotherapy without surgery as control group.

In fact, an important difference between lumpectomy and mastectomy groups was the number of women reporting neck and shoulder/axillary pain and the intensity of the pain which was greater in the mastectomy group. Further, the intensity of perceived neck and shoulder/axillary pain was associated with a greater sensitization (lower PPT over tibialis anterior muscles) within the mastectomy, but not the lumpectomy group. These findings support that lumpectomy, when indicated, would be preferred instead mastectomy for avoiding pain.

Conclusion

The current study found widespread pressure pain hyperalgesia in women who had received breast cancer surgery, suggesting central sensitization. In fact the degree of central sensitization was similar between lumpectomy and mastectomy. Nevertheless, the number of women reporting neck and shoulder/axillary pain, and the intensity of the pain which was greater in the mastectomy group Finally, PPTs over some areas were negatively associated with the intensity of pain in the mastectomy group suggesting a role of peripheral nociception in this surgical procedure.

Acknowledgments

The study was funded by a project grant from the Carlos III Health Institute, Ministry of Science, Spanish Government (FIS 08-ETES-PI0890418).

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PAPER III

The influence of patient attitude toward massage on pressure pain sensitivity and immune system after application of myofascial release in breast cancer survivors: A randomized controlled crossover study.

Fernández-Lao C, Cantarero-Villanueva I, Díaz-Rodríguez L, Fernández-de-las-Peñas C, Sánchez-Salado C, Arroyo-Morales M.

J Manipulative Physiol Ther

Journal Citation Reports Area
Integrative & Complementary Medicine: 9/21 Q2

First published: Oct 2011

The Influence of Patient Attitude Toward Massage on Pressure Pain Sensitivity and Immune System after Application of Myofascial Release in Breast Cancer Survivors: A Randomized, Controlled Crossover Study

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Abstract

Objective: The purpose of this study was to evaluate the influence of patient's attitudes toward massage on pressure pain sensitivity and the immune effects of myofascial release in breast cancer survivors (BCS).

Methods: Twenty BCS participated. They presented to the laboratory at the same time of the day on 2 occasions separated by 2 weeks. At each session, they received either a myofascial release technique or control (special attention) intervention. Salivary flow rate, cortisol and immunoglobulin A (IgA) concentrations, and α-amylase activity were obtained before and immediately after intervention from saliva samples. Pressure pain thresholds (PPT) over the cervical spine and temporalis muscle were assessed bilaterally. The attitude toward massage (ATOM) scale was collected before the first session in all BCS.

Results: The analysis of covariance revealed a significant intervention × time interaction for salivary flow rate ($P = .010$), but not α-amylase ($P = .111$), IgA ($P = .655$), and cortisol ($P = .363$) in favor of the experimental group: BCS exhibited an increase of salivary flow rate after myofascial release intervention. When the ATOM scale was included in the analysis, significant influence on IgA ($P = .001$) was found: BCS with positive attitude had a significant increase in IgA ($P > .05$). The analysis of covariance did not find a significant intervention × time interaction for PPT over the cervical spine or temporalis muscle, with no effect of ATOM scales for PPT ($P > .05$).

Conclusion: The current study suggests that myofascial release may lead to an immediate increase in salivary flow rate in BCS with cancer-related fatigue. We also found that the effect of myofascial release on immune function was modulated by a positive patient's attitude toward massage. (J Manipulative Physiol Ther 2011;xx:1-7)

Key Indexing Terms: *Attitudes; Manual Therapy; Breast Neoplasms; Immune System*

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Paper submitted June 20, 2011; in revised form July 7, 2011; accepted July 13, 2011.

0161-4754/$36.00

doi:10.1016/j.jmpt.2011.09.011

Massage is broadly used by patients with breast cancer during different phases of the condition; however, evidence suggesting that massage is an effective option for breast cancer survivors (BCS) is inconclusive.[1] One possible reason for the lack of evidence for massage in patients with breast cancer may be that there are only few studies and anecdotal information investigating short-term effect of massage in this population.[1] Moyer et al[2] have discussed the analgesic effects of massage and found that massage decreases pain. In addition, reflexology has proved to be effective for decreasing pain in patients with cancer,[3-5] but only 1 previous randomized clinical trial has suggested an effect for whole body massage in bodily pain in patients with breast cancer.[6] Jane et al[7] have recently postulated positive analgesic effects of massage in different oncology processes, whereas Sturgeon et al[8] reported no effects. Discrepancies between reviews support the necessity for conducting more studies on this topic.

It has been recently reported that BCS also exhibit widespread pressure pain hypersensitivity.[9,10] Some studies have demonstrated that the application of myofascial release exerts hypoalgesic effects in different conditions.[11-14] In fact, patients feel that massage therapy produces relaxation and reduces muscle tension.[15] It is possible that myofascial techniques may decrease pressure pain hypersensitivity in BCS, but no study has previously investigated this hypothesis.

In a cancer setting, massage has also shown effects within the immune system as an increase in the number of lymphocytes,[16] and natural killer cells[17] have been found after its application. However, a recent study has not confirmed the improvement of immune function induced by massage.[18] Changes in immune function by analyzing salivary markers such as immunoglobulin A (IgA) or α-amylase activity have been previously studied in other populations,[19,20] but not in BCS. Cortisol concentration and α-amylase activity are markers of stress response that are altered in BCS.[21] It would be interesting to investigate changes in immune system in BCS after the application of myofascial release.

Finally, it seems that the experience of cancer symptoms as pain is a result of the complex processing of information relayed to the brain from the sensory periphery and other aspects such as cognitive and emotional processing.[22] Interestingly, one of the more frequently postulated reasons for the use of different forms of complementary alternative medicine in BCS is to strengthen the immune system and improve the ability to relax muscles within the pain area.[23] This type of belief and the patient's attitude toward a therapeutic modality such as myofascial release could influence the effects of this therapeutic intervention.

We postulated that BCS who had a positive attitude to massage would be more likely to experience greater improvements than those with a negative attitude. To the best of the authors' knowledge, no previous studies have investigated the modulating effect of a patient's attitude toward massage on myofascial release in BCS. Therefore, the aim of the current study was to evaluate the influence of the patient's attitude toward massage on pressure pain sensitivity and the immune effects of myofascial release in BCS.

Methods

This study used a randomized single-blind, placebo-controlled crossover design to accommodate for possible interindividual variability in the outcome measures.

Participants

Twenty BCS were recruited, by an oncology nurse, from the Breast Oncology Unit–Hospital Virgen de las Nieves, Granada, Spain, from June 2009 to 2010. They were included if they (1) had a diagnosis of breast cancer (I-IIIA), (2) were between 25 to 65 years old, (3) had finished coadjuvant oncology treatment, and (4) had moderate to high fatigue assessed by the Fatigue Piper Scale[24] (>6 points) during the preceding week. They were excluded if they were receiving chemotherapy or radiotherapy treatment at the time of the study. Ethical approval for the study was granted by the ethics committee of the Hospital Virgen de las Nieves, Spain. All participants read and signed an informed consent form before their inclusion.

Study Protocol

Subjects were required to present to the laboratory at the same time of the day on 2 sessions separated by a 3-week interval. All sessions took place between 10 to 12 AM to avoid possible circadian rhythm–induced variations after previous studies on the physiologic effects of myofascial release.[12] Patients were asked to avoid exercise on the day before the study and were instructed not to consume food, caffeine, or alcoholic drinks during the 3 hours preceding the session. They were randomly assigned, by a coin flip, to either experimental (myofascial release) or placebo (educational session on healthy lifestyle) session by a clinician blinded to the assessment and outcomes. All sessions were conducted in a physical therapy university clinic with a thermostatically controlled temperature (20°-22°C).

Interventions

Each intervention was administered by a therapist with more than 5 years of experience in manual therapy, and more than 3 years treating BCS.

Within the experimental session, patients received a myofascial release protocol focused on the neck and shoulder area for 40 minutes (duration adapted to the patient' tissue response) after the Barnes approach.[25] The protocol included longitudinal strokes, J stroke, suboccipital pressure, frontalis bone spread, and ear pull technique.

The control condition consisted of a 40-minute educational session on healthy lifestyles with a focus on nutrition, relaxation techniques such as grade motor imagery, or dosage of physical exercise for breast cancer survivor. An adequate wash-up period of 3 weeks between the 2 sessions was established.

Pressure Pain Thresholds

Pressure pain thresholds (PPT) were the main outcome measure for this study. Pressure pain threshold is defined as the minimal amount of pressure where a sensation of pressure first changes to pain.[26] An electronic handheld pressure algometer (Somedic, Hörby, Sweden) consisting of a "pistol" handle and a rod with a pressure-sensitive gauge strain at the tip was used. Pressure pain threshold was assessed by a clinician blinded to group' allocation. Pressure pain threshold measurements were taken over the articular pillar of C5-C6 zygapophyseal joint (cervical) and over the temporalis muscle. The cervical spine was selected because hypersensitivity has been previously found in BCS.[9,10] The temporalis muscle was selected because it is susceptible to increased contraction in response to stress.[27,28] The mean of 3 trials was calculated and used for the analysis. A 30sec resting period was allowed between each trial. The reliability of pressure algometry has been found to be high (intraclass correlation coefficient [ICC]: 0.91; 95% confidence interval [CI], 0.82-0.97).[29]

Attitudes Toward Massage Scale

A 9-item measure of overall patient attitudes toward massage (ATOM) that includes 2 distinct subscales assessing the attitudes of massage as healthful (ATOM-MH) and massage as pleasant (ATOM-MP) was used. Items were concerned with ATOM and consisted of a stem in the form of a sentence with 5 ordered category response options ranging from "strongly disagree" to "strongly agree" with a middle option of "neutral." These subscales have shown adequate reliability (α = .70-.80).[30]

Saliva Sample

Saliva samples were collected from each participant for assessment of hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system, and immune system functions according to standardized procedures.[31] Saliva was collected into a collection tube (passive drooling technique). Particular care was considered when collecting saliva to avoid collection immediately after mouth cleaning, meals, snacks, or medications.

The process was done for 3 minutes. All saliva sampling was performed between 10 to 12 AM and always 4 hours after waking to control for possible fluctuation associated with daily output and diurnal rhythms on cortisol and α-amylase secretions.[31] It has been found that 4 hours after waking, α-amylase secretion reaches its highest level of the day. Participants were asked to refrain from eating, drinking, or chewing gum for 1 hour before sampling. They were also asked to refrain from brushing their teeth in the morning before saliva sampling. The volume of the sample was calculated (nearest 0.1 mL), and saliva flow rate ($mL \times min^{-1}$) was determined by dividing the volume of saliva by the collection time. Immediately after collection, saliva samples were centrifuged at 3000 rpm for 15 minutes to remove any sediment and were stored at −70°C until analysis. Concentration of cortisol and IgA and α-amylase activity were assessed in thawed samples by an assessor blinded to group' allocation.

Saliva was collected at preintervention and immediately after the intervention. Salivary cortisol and IgA concentrations, and α-amylase activity were calculated using a commercial luminescence immune assay (Salimetrics, State College, PA), reading the luminescence units with automatic luminometers (Sunrise; TECAN Group, Mannedorf, Switzerland). Saliva samples were analyzed in a single batch to eliminate interassay variance, and they were measured in duplicate. In fact, adequate intraassay accuracy was obtained with a coefficient of variance less than 8.5%.

Sample Size Calculation

Sample size determination was performed with appropriate software (Tamaño de la Muestra1.1, Madrid, Spain). The calculation was based on detecting between-sessions clinical differences of 20% on PPT[32] with an α level of .05, a desired power of 80%, and an estimated interindividual coefficient of variation of 20%. This generated a sample size of at least 16 participants.

Statistical Analysis

Data were analyzed with SPSS version 19.0 (SPSS Inc, Chicago, Ill). Mean, standard deviations, and 95% CIs of the values were calculated for each variable. The Kolmogorov-Smirnov test showed a normal distribution ($P > .05$). Preintervention data before each session were compared using independent t tests. A 2-way repeated-measures analysis of covariance, with session (control, experimental) as between-subjects variable, time (pre-post) as within-subjects variable, and ATOM (ATOM-MH/ATOM-MP) as covariate, was used to examine the effects of interventions. Separate analyses of covariance were performed with each dependent variable. The hypothesis of interest was group × time interaction, with an ATOM subscale interaction. $P < .05$ was considered statistically significant.

Results

Demographic Data

Twenty BCS during their first year after treatment with a mean age of 49 ± 8 years were included. They had university-level education (40%), were married (80%), white, and from a metropolitan area. Eighteen (90%) participants had breast cancer stage I or II and had received both radiation and chemotherapy as adjuvant treatment after surgery (80%). Fourteen (70%) had received lumpectomy, whereas the remaining 6 (30%) had received mastectomy. In addition, 16 (80%) women were taking antagonist of estrogen receptors or aromatase inhibitors drugs, whereas 10% were taking monoclonal antibody HER2. None of the participants had received rehabilitation treatment. Three participants (15%) were taking analgesics (ibuprofen or acetaminophen).

Table 1. *Preintervention, postintervention and change scores of salivary flow rate, α -amylase activity, cortisol, and IgA concentrations*

	Control session	Myofascial release session
Salivary flow rate (mL × min^{-1})		
Before intervention	1.3 ± 0.5 (95% CI, 1.0-1.6)	1.2 ± 0.5 (95% CI 1.0-1.4)
After intervention	1.3 ± 0.5 (95% CI, 1.0-1.5)	1.5 ± 0.5 (95% CI 1.2-1.7)
Pre-post differences	0.0 (95% CI, 0.1/0.1)	0.3 (95% CI, 0.2/0.4) [a]
α-Amylase activity (U × min^{-1})		
Before intervention	159.9 ± 85.1 (95% CI, 118.9-200.9)	162.1 ± 79.0 (95% CI, 123.9-200.1)
After intervention	225.3 ± 106.3 (95% CI, 174.0-276.5)	287.7 ± 162.2 (95% CI, 209.5-365.9)
Pre-post differences	65.4 (95% CI, 35.9/94.7)	125.6 (95% CI, 57.7/193.6)
Cortisol concentration (μg × min^{-1})		
Before intervention	0.3 ± 0.2 (95% CI, 0.2-0.4)	0.3 ± 0.1 (95% CI, 0.2-0.4)
After intervention	0.2 ± 0.1 (95% CI, 0.1-0.3)	0.2 ± 0.2 (95% CI, 0.1-0.3)
Pre-post differences	−0.1 (95% CI, −0.2/0.1)	−0.1 (95% CI, −0.2/0.1)
IgA concentration (mg × min^{-1})		
Before intervention	16.5 ± 7.5 (95% CI, 12.7-20.4)	15.5 ± 7.2 (95% CI, 11.8-19.2)
After intervention	19.1 ± 10.2 (95% CI, 13.9-24.4)	21.8 ± 12.8 (95% CI, 15.2-28.4)
Pre-post differences	2.6 (95% CI, −1.4/6.7)	6.3 (95% CI, 1.3/11.2) [b]

Values are expressed as mean ± SD for pre- and postintervention data and as mean (95% CI) for within- and between-group change scores.

[a] Statistical significant differences between sessions without ATOM influence ($P < .05$).

[b] Statistical significant differences between sessions with ATOM-MP influence ($P < .05$).

Preintervention data for each variable were not significantly different between each treatment session: PPT cervical affected side ($P = .130$), cervical nonaffected side ($P = .306$), temporalis affected side ($P = .167$), temporalis nonaffected side ($P = .089$), salivary flow rate ($P = .225$), α-amylase activity ($P = .859$), cortisol ($P = .750$), and IgA ($P = .533$) concentrations.

Effects of Myofascial Release on Salivary Markers

The analysis of variance revealed a significant intervention × time interaction for salivary flow rate (F = 8.587; $P = .010$) but not for α-amylase activity (F = 2.960; $P = .111$), IgA concentration (F = 0.210; $P = .655$), and cortisol concentration (F = 0.892, $P = .363$). Pairwise comparisons revealed that BCS exhibited significant increases in salivary flow rate ($P = .005$) after the myofascial release intervention, with no changes after the control intervention ($P = .244$). When the ATOM-MP subscale was included in the analysis, a significant influence for IgA (F = 20.001, $P = .001$) was found: BCS with a positive attitude toward massage experienced greater increases in IgA. The attitude scale did not influence cortisol concentration (ATOM-MP: $P = .744$; ATOM-MH: $P = .711$) or α-amylase activity (ATOM-MP: $P = .676$; ATOM-MH: $P = .983$). Table 1 summarizes pre- and postintervention scores of each salivary marker for both sessions.

Effects of Myofascial Release on PPTs

The analysis of variance did not find an intervention × time interaction for PPT over the cervical spine (affected side: F = 0.003, $P = .957$; nonaffected side: F = 0.931, $P = .351$) or the temporalis muscle (affected side: F = 0.160, $P = .694$; nonaffected side: F = 0.016, $P = .990$). There were also no significant attitude scale–influenced changes in PPT levels over temporalis muscle ($P = .245$) and over cervical spine ($P = .441$). Table 2 details pre- and postintervention scores of PPT for both the temporalis muscle and the cervical spine. No adverse effects associated with the myofascial release were reported.

Discussion

This is the first study investigating the influence of a patient's attitude toward massage on pressure sensitivity and immune system function after myofascial release in breast cancer survivor. We found a significant increase in salivary flow rate, not modulated by patient's attitude, and an increased in IgA concentration, influenced by a positive patient's attitude relative to the pleasant effects of massage. No changes in pressure pain sensitivity were found.

Salivary flow rate is a marker of vegetative influence in stress situations.[33,34] Our results support a parasympathetic effect of the myofascial release intervention when applied on BCS, which agree with previous studies related to physical stress situations[19] and pain conditions.[35] Physiologic mechanisms implied by these results are not currently understood. It is possible that the parasympathetic response may be mediated by the stimulation of type 3 and 4 mechanoreceptors during myofascial release interventions.[36] These mechanoreceptors exhibit a relationship with the autonomic nervous system, which is able to trigger the response of salivary glands. These results may stimulate research focused on long-lasting effects of myofascial release in BCS, particularly in subgroups of patients having Sjögren syndrome associated with adjuvant hormone therapy[37] or xerostomy after cancer treatment.[38]

Table 2. *Preintervention, postintervention, and change scores of PPTs (kPa) in temporal and cervical muscles*

	Control session	Myofascial release session
Temporalis muscle affected side		
Before intervention	214.9 ± 56.9 (95% CI, 188.2-241.5)	194.9 ± 56.0 (95% CI, 168.7-221.2)
After intervention	216.5 ± 59.5 (95% CI, 188.4-244.1)	196.5 ± 63.4 (95% CI, 166.8-226.2)
Pre-post differences	1.6 (95% CI, −27.5/24.8)	1.6 (95% CI, −10.9/13.1)
Temporalis muscle unaffected side		
Before intervention	213.4 ± 64.8 (95% CI, 183.0-243.7)	192.3 ± 59.7 (95% CI, 164.3-220.4)
After intervention	215.3 ± 49.9 (95% CI, 192.0-238.7)	203.3 ± 61.9 (95% CI, 174.3-232.3)
Pre-post differences	1.9 (95% CI, −18.5/22.1)	11.0 (95% CI, 1.46/23.5)
Cervical spine affected side		
Before intervention	188.7 ± 58.4 (95% CI, 161.4-216.0)	204.5 ± 73.3 (95% CI, 170.1-238.8)
After intervention	193.7 ± 56.3 (95% CI, 167.4-220.1)	215.3 ± 63.8 (95% CI, 185.5-245.1)
Pre-post differences	5.0 (95% CI, −9.4/19.6)	10.8 (95% CI, −13.9/35.6)
Cervical spine unaffected side		
Before intervention	204.5 ± 81.6 (95% CI, 166.3/242.6)	184.4 ± 68.8 (95% CI, 152.2-216.6)
After intervention	210.7 ± 55.5 (95% CI, 184.7/236.7)	193.1 ± 76.9 (95% CI, 157.0-229.1)
Pre-post differences	6.2 (95% CI, −24.9/38.0)	8.7 (95% CI, −9.6/27.0)

Values are expressed as mean ± SD for pre- and postintervention data and as mean (95% CI) for within- and between-group change scores.

Our results did not support the ability of myofascial release to improve immune function or improve cortisol and α-amylase activity in BCS having cancer-related fatigue. These findings agree with a recent meta-analysis that did not find effects for different forms of massage on cortisol concentrations.[39] Nevertheless, the results of our study are contrary to those reported for reflexology where changes in α-amylase-activity[40] were found, but in line with a previous study on healthy people where changes in α-amylase-activity were not reported.[20] However, one of the more relevant findings of our study is the influence of the patient's attitude toward massage on the ability of myofascial release to improve IgA concentrations in BCS. In fact, 50% to 75% of BCS during first year after treatment use different forms of alternative medicine because they believe that this can boost their immune system.[41] It is possible that BCS with a positive attitude toward the immune boosting effects of massage may be more susceptible to the relaxation effects of myofascial release. A relaxation response has been previously associated with increases in IgA after different therapeutic modalities.[42,43] These findings are extremely helpful for clinicians who apply specific manual therapies adapted to their patient's attitudes, especially by inexperienced recipients. Current findings warrant future studies for identifying long-term effects of myofascial release in immune function in different attitude subgroups of BCS.

An interesting finding was that we did not observe any change in pressure hypersensitivity after myofascial release in our sample of BCS. Furthermore, attitude did not appear to exert any significant effect on pressure pain sensitivity. It is possible that one treatment session may not be enough to activate pain inhibitory mechanisms in BCS. Future studies investigating the cumulative effects of consecutive sessions of myofascial release applied on BCS on pressure sensitivity are needed.

Limitations

Some methodological limitations of the current study should be acknowledged. First, the same therapist performed all manual therapy interventions that may limit the generalizability of the results. It would be expected that other clinicians may be able to provide similar treatments with similar results. Second, we investigated the short-term effects of myofascial release, which may have limited clinical relevance at this moment. It is possible that subsequent sessions may induce longer-lasting effects. Third, alterations of stress response, that is, a flattened diurnal cortisol slope[44] present in BCS having cancer-related fatigue could reduce the ability of myofascial release in changing salivary cortisol concentrations and α-amylase activity. Future studies including cortisol slope changes and other HPA-axis biomarkers altered during breast cancer treatment, such as serotonin, should be conducted to investigate the ability of myofascial release to affect endocrine function in this population. Fourth, we cannot exclude the placebo effect associated with hands-on techniques. Future studies should compare different manual techniques to placebo interventions including manual contact on the patient. Finally, we should recognize that blinding patients may be not effective because the placebo intervention was different from the treatment. Therefore, the placebo effect associated with hands-on technique should not be ignored in studies testing the influence of patients' attitudes in relation to myofascial release.

Conclusions

The current study suggests that myofascial release may lead to an immediate increase in salivary flow rate in BCS. In addition, myofascial release induces an effect on immune function by increasing IgA, but this effect is modulated by a patient's positive attitude toward massage.

Clinicians should be aware of the interaction between effects of different manual therapies used for the management of BCS and the personal attitudes of the patients to the technique itself.

Practical Applications

- This study showed that myofascial release leads to an immediate increase of salivary flow rate in BCS, suggesting a parasympathetic effect of the intervention.
- Myofascial release induced an effect in immune function by increasing the concentrations of immunoglobulin A, but this effect was modulated by a positive attitude toward massage from the patients.
- For this study, a session of myofascial release was not able to decrease pressure pain sensitivity in BCS.

Funding Sources and Potential Conflicts Of Interest

The study was funded by a research project grant (FIS PI10/02749) from the Health Institute Carlos III and PN I+D+I 2008-2011, Madrid, Spanish Government, and a grant of Andalusian Health Service, Junta de Andalucia (PI-0457-2010). No conflicts of interest were reported for this study.

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PAPER IV

Attitude towards massage modify effects of myofascial release in breast cancer survivors: A randomized clinical trial with crossover design.

Fernández-Lao C, Cantarero-Villanueva I, Díaz-Rodríguez L, Cuesta-Vargas AI,
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Eur J Canc Care

Journal Citation Reports Area
Rehabilitation: 26/44 Q3

First Published: 2011 Nov

PAPER III

The influence of patient attitude toward massage on pressure pain sensitivity and immune system after application of myofascial release in breast cancer survivors: A randomized controlled crossover study.

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J Manipulative Physiol Ther

Journal Citation Reports Area
Integrative & Complementary Medicine: 9/21 Q2

First published: Oct 2011

CONCLUSIÓN/CONCLUSION

CONCLUSIONES

- Nuestros resultados revelan una hipersensibilidad bilateral generalizada al dolor por presión en pacientes con dolor postmastectomía. Además, el dolor local y referido provocado por los PG activos reproduce las molestias en cuello y los hombros /zona axilar en estas pacientes. Estos resultados sugieren un mecanismo de sensibilización central y periférica, en pacientes con dolor postmastectomía. (Artículo I)

- Existe una hiperalgesia generalizada al dolor por presión en las mujeres sometidas a cirugía por cáncer de mama, lo que sugiere una sensibilización central generalizada. Sin embargo, el número de mujeres que tienen dolor de cuello y hombro / zona axilar, y la intensidad del dolor fue mayor en el grupo de la mastectomía que en el grupo de lumpectomía. Por último, los UDP en algunas zonas se asociaron negativamente con la intensidad del dolor en el grupo de mastectomía, lo que existe un proceso de nocicepción periférica en este procedimiento quirúrgico. (Artículo II)

- La liberación miofascial puede conducir a un aumento inmediato del flujo de secreción salival en MSCM con fatiga relacionada inducida por el cáncer. Además el efecto de la liberación miofascial en la función inmunológica es modulada por la actitud positiva de las pacientes hacia el masaje/terapia manual. (Artículo III)

- El masaje/terapia manual puede conducir a un aumento inmediato de la VFC asociada con una mejoría del estado de ánimo en MSCM que sufren fatiga asociada al cáncer. Se demuestra que el impacto positivo del masaje en el estado de ánimo puede ser modulado por la actitud hacia el masaje, de forma que una actitud positiva hacia el masaje se asocia con una mayor mejoría en el estado de ánimo. (Artículo IV)

Nuestros hallazgos ayudan a esclarecer los mecanismos de producción del dolor postmastectomía y apoyan el uso del masaje/terapia manual en el manejo de los síntomas asociados al cáncer de mama.

CONCLUSIONS

I. Our findings revealed bilateral widespread pressure pain hypersensitivity in patients with postmastectomy pain. In addition, the local and referred pain elicited by active TrPs reproduced neck and shoulder/axillary complaints in these patients. These results suggest both peripheral and central sensitization mechanism in patients with postmastectomy pain. **(Paper I)**

II. It was found widespread pressure pain hyperalgesia in women who received breast cancer surgery suggesting central spreading sensitization. Nevertheless, the number of women reporting neck and shoulder/axillary pain, and the intensity of the pain was greater in the mastectomy group than the lumpectomy group. Finally, PPTs over some areas were negatively associated with the intensity of pain in the mastectomy group suggesting a role of peripheral nociception in this surgical procedure. **(Paper II)**

III. Myofascial release may lead to an immediate increase in salivary flow rate in BCS with cancer-related fatigue. We also found that the effect of myofascial release on immune function was modulated by a positive patient's attitude toward massage/manual therapy. **(Paper III)**

IV. Massage/manual therapy may lead to an immediate increase of HRV associated with a mood improvement in BCS suffering CRF. We show that the positive impact of massage in mood can be modulated by health and pleasure attitude to massage, as a positive attitude towards massage was associated with a greater improvement in mood. **(Paper IV)**

Our findings help to highlight the mechanism of postmastectomy pain and support the use of massage/manual therapy techniques in the management of breast cancer related symptoms.

AGRADECIMIENTOS/ACKNOWLEDGEMENTS

A estas alturas no es necesario decir que esta tesis no habría sido posible sin el trabajo de muchas personas, no solo en forma de aportaciones científicas y profesionales sino también personales. Gracias a todos.

Quiero mostrar mi profundo agradecimiento a mis padres, por seguir aquí, por vuestro inestimable "ejemplo de vida", vuestra fortaleza ante la adversidad y por ser como sois, sin más. Sois los mejores padres que se pueden tener.

A mi padre, por su apoyo, rectitud y cariño durante toda mi vida, porque sin todo eso y sin su ejemplo, hoy no sería la persona que soy. Porque en mitad del proceso de elaboración de esta tesis sobre el cáncer nos dio una lección de superación y fortaleza, gracias por tus ganas de vivir y por ser el ejemplo más valioso que he tenido en la vida.

A mi madre, porque luchó de una forma sobrehumana para quedarse con nosotros. Por ser la mejor persona que he tenido nunca cerca, por el amor que desprende, por tener siempre el mejor consejo preparado y por ser el espejo en el que mirarme.

A mi "hermanito", por ser el mejor compañero durante mi niñez y adolescencia, por tener siempre una sonrisa que regalarme cuando las cosas no van bien, por compartirlo todo conmigo y ser un modelo de "filosofía de vida".

A Nilo, por ser el perfecto compañero de vida. Por comprenderme en cada momento que le he robado por esta tesis, por los viajes, los congresos, los meses separados…por hacerme sentir que está orgulloso de mí. Por ser el mejor apoyo en los momentos duros y la mejor compañía para celebrar los momentos felices.

A mi familia y amigos (no los nombro a todos porque la lista sería interminable), por su cariño, por todos esos momentos de “desconexión” y por no dejarme sentir nunca sola. Gracias a todos los que me enseñaron a no tirar la toalla ante la adversidad.

A todos los que ya no están, porque aunque me hubiese gustado compartir esto con ellos, sé que donde estén, se sentirán orgullosos.

A mis directores de tesis. En primer lugar Manuel Arroyo, por darme la oportunidad de unirme a este proyecto, por ser el mejor maestro que haya podido tener, por ser el alma y el cerebro de todo esto, por el permanente sustento y dedicación. Por tener siempre la ambición necesaria, ser el ejemplo al que seguir, la figura que admirar y el amigo con el que compartir.

En segundo lugar a César Fernández, porque en la distancia ha sido un magnífico ejemplo y un apoyo importante, por creer siempre en nuestro proyecto, sustentarlo e impulsarlo, por los buenos consejos, por soportar los “fueras de plazo” y por hacernos reír tanto.

A Irene, mi cómplice en todo este “lío”, porque sin su tenacidad, su profesionalidad, su energía, su entusiasmo y apoyo, hoy no estaríamos aquí con el trabajo terminado. Gracias por enseñarme tanto, por ser tan generosa y por todas las experiencias vitales que hemos compartido.

A todos mis compañeros y amigos del Departamento de Fisioterapia por su ayuda, cariño y ejemplo de dedicación a nuestro trabajo.

A mis compañeros y amigos del grupo de investigación BIO-277 por los momentos de preparación de nuestros respectivas investigaciones juntos en el laboratorio, en los pasillos, en la cafetería…

A todas las mujeres que forman parte de esta tesis, a las que han sufrido el cáncer y a las que no, por prestarnos siempre su ayuda desinteresada. Ellas son la razón de ser de esta investigación y las destinatarias de todo el esfuerzo, que espero, les sea útil. Por darnos una lección de fuerza, entereza e ilusión en la vida. Gracias a todas.

CURRICULUM ABREVIADO/SUMMARIZED CV

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Diplomatura en Fisioterapia

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Fecha de obtención: Junio 2003

Licenciatura en Documentación

Facultad de Biblioteconomía y documentación. Universidad de Granada.

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Master Universitario en Antropología Física y Forense

Departamento de Antropología Física y Forense. Facultad de Medicina.

Universidad de Granada

Fecha de Obtención: Septiembre 2008

Master Universitario en Información Científica. Acceso, evaluación y tratamiento.

Facultad de Comunicación y Documentación. Universidad de Granada

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DOCENCIA UNIVERSITARIA REGLADA

Curso 2007-2008

Profesora asociada Tipo I con dedicación a 3 horas desde el 28 de Noviembre de 2007 hasta el 9 de Enero de 2008. Departamento de Fisioterapia. Asignatura: Fisioterapia para Nutrición.

Curso 2008

Profesora Asociada Tipo I con dedicación a 6 horas desde el 9 de enero de 2008 hasta Octubre de 2008. Departamento de Fisioterapia. Asignaturas: Fisioterapia General, Fisioterapia para enfermería.

Cursos 2009-2012

Personal Docente e Investigador con dedicación a tiempo completo desde abril de 2009. Departamento de Fisioterapia. Asignaturas: Fisioterapia General, Estancias Clínicas I, Fundamentos de Fisioterapia.

DOCENCIA UNIVERSITARIA NO REGLADA

Curso 2008/2009

Profesora Invitada. Curso Nacional de Actualización en el Tratamiento Fisioterapéutico de las lesiones tendinosas. Aula Permanente de Mojacar. Facultad de Ciencias de la Salud. Universidad de Granada. Mayo 2009

Curso 2009/2010

Ponente. Jornadas: "El deporte, una actividad física sostenible y saludable". Facultad de Ciencias. Universidad de Granada. Abril 2010

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Curso	**Iniciación a la docencia universitaria**
Organismo	Vicerrectorado para la Garantía de la Calidad. Universidad de Granada.

Duración 200 horas

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ACTIVIDAD INVESTIGADORA

Participación en Proyectos y Contratos de Investigación

- **PROYECTO:** *E-CUIDATE: Eficacia sobre el dolor musculoesquelético de una plataforma de telefisioterapia en mujeres con cáncer de mama.* Entidad Financiadora: Fondo de Investigaciones Sanitarias. Instituto de Salud Carlos III. Investigador Principal: Manuel Arroyo Morales. (2011-2013)
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- **PROYECTO:** *Utilización de la imagen ecográfica para el desarrollo de competencias de tratamiento del control motor en pacientes con lumbalgia.* Entidad Financiadora: Unidad de Innovación Docente. Universidad de Granada. Investigador Principal: Manuel Arroyo Morales. (2011-2012)
- **Contrato de Investigación:** "*Estudio de los parámetros funcionales para la prevención laboral activa: Prevención de lesiones, recuperación-readaptación del sistema músculo-esquelético, y acondicionamiento físico integral a través de un sistema funcional específico para los especialistas en prevención y extinción de incendios forestales*"**.** Empresa Financiadora: Oficina de Transferencia de Resultados de Investigación UGR. Investigador Responsable: Manuel Arroyo Morales. (2011)
- **Contrato de Investigación:** "*Estudio de los parámetros funcionales para la prevención laboral activa: Prevención de lesiones, recuperación-readaptación del sistema músculo-esquelético, y acondicionamiento físico integral a través de*

un sistema funcional específico para los especialistas en prevención y extinción de incendios forestales". Empresa Financiadora: Oficina de Transferencia de Resultados de Investigación UGR. Investigador Responsable: Manuel Arroyo Morales. (2010)

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- **PROYECTO:** *Efectos Psicofisiológicos y sobre la Supervivencia de la Cinesiterapia Activa y la Masoterapia en Supervivientes de Cáncer de Mama*. Entidad financiadora: Fondo de Investigaciones Sanitarias. Instituto de Salud Carlos III. Investigador Principal: Manuel Arroyo Morales. (2009-2010)

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Capítulos de libros y Monografías

- **CAPÍTULO DE LIBRO:** *Estudio de la satisfacción de los alumnos de Fisioterapia sobre la plataforma web ecofisio para la integración del a imagen ecográfica.* Carolina Fernández-Lao, Irene Cantarero-Villanueva, Eduardo Castro-Martín, Lourdes Díaz-Rodríguez, Miguel Guirao-Pyñeiro, Manuel Arroyo-Morales. VIII Foro sobre la evaluación de la calidad de la investigación y de la educación superior (FECIES). Santander, 2011. ISBN: 978-84-694-3488-8.
- **CAPÍTULO DE LIBRO:** *La comunicación como competencia en los docentes*. Lourdes Díaz Rodríguez, Irene Cantarero Villanueva, Carolina Fernández-Lao, Javier Ramos Torrecillas, De Luna Bertos Elvira, Olga García Martínez. VIII Foro sobre la evaluación de la calidad de la investigación y de la educación superior (FECIES). Santander, 2011. ISBN: 978-84-694-3488-8.
- **CAPÍTULO DE LIBRO**: *Percepción del alumnado en torno al uso de las TICs para el desarrollo de competencias en valoración del aparato locomotor.* Irene Cantarero-Villanueva, Carolina Fernández-Lao, Lourdes Díaz- Rodríguez, Eduardo Castro-Martín, Bernabé Esteban-Moreno, Manuel Arroyo-Morales. VIII Foro sobre la evaluación de la calidad de la investigación y de la educación superior (FECIES). Santander, 2011. ISBN: 978-84-694-3488-8.
- **MONOGRAFÍA:** Bases científicas y entrenamiento específico en la prevención laboral activa. Control motor y condición física para el personal de prevención y extinción de incendios forestales. Editorial AIFEMA, 2010. Granada ISBN: 978-84-614-3955-3

- **CAPÍTULO DE LIBRO: La evaluación de las competencias: un logro a alcanzar.** Evaluación de la Calidad de la Educación Superior y de la Investigación. Murcia, 2010. ISBN: 978-84-693-2096-9

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- **Primer premio de Investigación 2011 del Ilustre Colegio de fisioterapia de Andalucía**: *Influencia de las actitudes de los pacientes sobre la terapia manual en mujeres con fatiga inducida por cáncer de mama: un diseño cruzado aleatorizado con enmascaramiento simple*. Fernández-Lao C, Cantarero-Villanueva I, Arroyo-Morales M.

- **Galardón de Accesit de premio de Investigación 2010 del Ilustre Colegio de fisioterapia de Andalucía**: *Eficacia de un programa de Fisioterapia (Cuídate)*. Cantarero-Villanueva I, Fernández-Lao C, Arroyo-Morales M.

- **Primer premio comunicación presentada en las II Jornadas Internacionales y VI nacionales en ciencias de la Salud:** *Metodología de estudio de los desajustes del control motor en pacientes tratadas por cáncer de mama.* Galiano-Castillo N, Fernández Lao C, Cantarero Villanueva I, Olea Serrano N, Arroyo-Morales M. (2010).

- **Primer premio comunicación presentada en el XII Congreso Andaluz de Psicología de la Actividad Física y el Deporte:** *Estudio descriptivo del estado de ánimo en mujeres con cáncer de mama previo a un programa de cinesioterapia activa.* Cantarero Villanueva I., Fernández Lao C., Feriche-Fernández Castanys B., Arroyo Morales M. (2009)

Participación en Jornadas y Congresos

- La doctoranda ha participado como autora y coautora en más de 30 congresos nacionales e internacionales.

- La doctoranda ha participado en las II Jornadas Internacionales y VI nacionales en Ciencias de la Salud como miembro del Comité Organizador celebradas en la Universidad de Granada.