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Far infrared ray (FIR) therapy: An effective and oncological safe treatment modality for breast cancer related lymphedema

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ABSTRACT

Background: The incidence of breast cancer related lymphedema is approximately 5%. Far infrared ray (FIR) treatment can potentially reduce fluid volume and extremity circumference as well as the frequency of dermatolymphangitis (DLA). However, there is no published data on the oncological safety of FIR and the potential for activation of any residual breast cancer cells. The aim of this study is to investigate the safety of far infrared ray (FIR) treatment of postmastectomy lymphedema, clinically and *in vitro*.

Methods: Patients who underwent mastectomy more than 5 years ago complicated by upper extremity lymphedema for more than 1 year were included. The enrolled patients were divided into an FIR treatment group and a control group (conservative treatment using bandage compression). Outcome measures included tumor markers (CA153, CA125), ultrasonography of relevant structures and monitoring for adverse reactions 1 year after treatment. For the *in vitro* part of the study, the effects of FIR on human breast adenocarcinoma cell lines (MCF7, MDA-MB231) compared to the effects of FIR on human dermal fibroblasts as a control were considered. The viability, proliferation, cell cycle and apoptotic statistics of the adenocarcinoma and human dermal fibroblast cell lines were analyzed and compared.

Results: Results demonstrated that after treatment with FIR, tumor marker (CA153, CA125) concentrations in both the FIR and control groups were not elevated. There was no statistically significant difference between FIR and control group marker expression ($p > 0.05$). Furthermore, no patients were diagnosed with lymphadenectasis or newly enlarged lymph nodes in these two groups. Importantly, there were no adverse events in either group. The *in vitro* experiment indicated that FIR radiation does not affect viability, proliferation, cell cycle and apoptosis of fibroblasts, MCF-7 and MDA-MB-231 cells.

Conclusions: FIR should be considered as feasible and safe for the treatment of breast cancer related lymphedema patients 5 years after mastectomy. FIR does not promote recurrence or metastasis of breast cancer and is a well-tolerated therapy with no adverse reactions.

1. Introduction

Breast cancer-related lymphedema (BCRL) of the upper limb is a well-recognized complication associated with breast cancer surgery, particularly when axillary lymph node clearance and irradiation are included as part of the treatment [1]. The frequency of postmastectomy lymphedema is described to be as high as 9–41% following axillary dissection and 4–10% following sentinel lymph node biopsy for breast

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cancer [2,3]. The affected patients have increased interstitial fluid (lymph) and develop chronic inflammation resulting in fibro-adipose tissue proliferation and deposition as well as nonpitting edema [4,5].

The clinical symptoms of postmastectomy lymphedema include: oedema of the upper extremity, poor skin elasticity and limited joint movements as well as dermato-lymphangitis (DLA) [6,7]. Excess tissue and fluid in the upper limb causes pain and anxiety, affects the patient's activities of daily living and social comfort, decreases physical function due to limb bulkiness and weight, leads to body image disturbances, and has a significant, measurable effect on quality of life [8].

Currently, conventional, non-surgical treatment for BCRL includes exercise and elevation, manual lymphatic drainage, hyperthermia, intermittent air pressure wave therapy, elastic bandage, elastic pants, elastic sleeves, low-level laser therapy, self-nursing, pharmacotherapy and static compression garments.

These methods aim to alleviate symptoms and may have beneficial effects in all clinical stages but it is nearly impossible to achieve significantly improved clinical outcomes utilizing these conservative measures alone. Conservative treatment protocols seem to be most effective in early stage lymphedema (International Society of Lymphology stages I and II). These treatments represent an important supplementary tool for patients who are not able or do not want to undergo surgical procedures [9–13], and may improve lymphedema by promoting collateral lymph flow and removing excess fat tissue thereby slowing down or even preventing the aggravation of pre-existing lymphedema.

Far Infrared Radiation (FIR) treatment affects tissues in a similar way as hyperthermia, acting *via* three main biological effects: radiation, vibration (or resonance), and a thermal effect. The infrared region of the spectrum of radiation lies beyond the red end of the visible range, with wavelengths between 0.01 and 7.5×10^{-5} cm. Infrared rays are further divided in: near infrared, medium infrared, and far infrared. Among the different frequencies composing the infrared spectrum, far infrared rays are the most beneficial for living organisms [14,15]. As the majority of human body mass is composed by 55%–60% of water, FIR is able to interact with water molecules and cause a thermal reaction which increases tissue temperature and dilates blood vessels. Far infrared rays are able to penetrate tissue layers up to 4 cm in depth and resonate with water and other organic molecules [16]. In this way, blood circulation is improved and a greater amount of oxygenized blood can reach the soft tissues, reacting with nutrients and removing the accumulated toxins.

These effects lead to clinical improvement of particular pathological modalities such as lymphedema, promoting microcirculation and collateral lymph flow [17]. FIR therapy has been applied to various clinical fields, including vessel-related disorders, [18] and more recently to thousands of patients affected by lymphedema [12,13,17]. It has been shown that FIR effectively reduces extremity fluid volume and circumference as well as the frequency of DLA [18]. However, the oncological safety of FIR has not been investigated yet, as there is a theoretical potential for activation of any residual breast cancer cells in the lymphedematous tissues. Breast cancer recurrence rates during FIR treatment of upper extremity lymphedema has also not been specifically looked at. The purpose of this study is to demonstrate the effectiveness and oncological safety of FIR to treat BCRL clinically and *in vitro*.

2. Patients and Methods

2.1. Clinical Study

63 female patients suffering from BCRL following modified radical mastectomy, axillary lymphadenectomy, and chemo-radiotherapy were randomised into two groups and treated between April 2014 and April 2016 using FIR ($n = 32$) and compression bandages ($n = 31$).

Only patients 5 years post-mastectomy and presenting with upper extremity lymphedema of more than 1 year were included in the study.

Patients with clinical evidence of potential cancer recurrence or those who suffered from serious comorbidities that could interfere with routine treatment and follow-up were excluded from the study. Furthermore, patients with episodes of DLA or vascular embolization and patients whose affected limbs were too large to be placed in the curing cabin were also excluded from the study.

2.1.1. FIR Therapy Device

The FIR therapy device was developed by the Ninth People's Hospital, affiliated with Shanghai Jiaotong University, China [19]. The infrared radiation producing elements are enclosed in a stainless steel chamber that is resistant to high temperatures. Inside the chamber, installed on an internal ring there are eight quartz lamp lights that emit infrared rays with a wavelength between 6.0 and 14.0 μm [14]. The device is also equipped with a temperature control apparatus that can adjust the temperature inside the chamber.

2.1.2. FIR Group Treatment Measures

Following written consent, FIR therapy was initiated. Treatment duration was 1 h every day for 4 weeks (20 days in total) at a temperature of 42 °C. Patients were advised to implement self-nursing skills such as extremity hygiene, prevention of skin injuries and the avoidance of dermatophytosis [19].

2.1.3. Control Group: Bandage Treatment Measures

Following written consent, compression bandage treatment was commenced. The patients wore bandages for 12 h each day, while awake. They were treated for 4 weeks (20 days in total). Patients were advised to implement self-nursing skills such as extremity hygiene, prevention of skin injuries and the avoidance of dermatophytosis.

2.1.4. Ethics Statement

Informed consent was obtained in writing before treatment. The ethics committee, Ninth People's Hospital, Shanghai, prospectively approved this research study. All relevant regulations, as well as the guidelines of the Declaration of Helsinki were followed accordingly.

2.1.5. Data Collection

Patients were followed up for 1 year after treatment. Follow-up outcome measures included: A) Tumor marker detection: Venous blood was extracted and tumor markers relevant to breast cancer were assayed in the laboratory. Results within normal range were recorded as (−). Results that were higher than normal range were scored as (+). Tested tumor markers were CA153 and CA125. Normal range for CA125 is 0-35 U/ml. Normal range for CA153 is 0-25 U/ml. B) Ultrasonography: The following organs and lymphatic basins were imaged: liver, spleen, kidney, breast, axillary lymph nodes, supra-clavicular and infra-clavicular lymph nodes. If lymphadenectasis was detected or newly enlarged lymph nodes were found in the liver, spleen, kidney, or breast, the case was recorded as (+). If not, it was registered as (−). C) Adverse reactions: If any adverse reaction, such as burns, local infection, pyrexia, discomfort, and pain, induced by FIR or compression bandage occurred, the case was recorded as (+). If no adverse reaction occurred, the case was recorded as (−).

2.2. The In Vitro Study

2.2.1. Cell Cultures

Dermal diploid fibroblasts were derived from 2-mm punch biopsies taken from the upper arms of healthy male donors. Human breast adenocarcinoma cell lines MCF-7 and MDA-MB231 were purchased from American Type Culture Collection (ATCC, USA). Cells were routinely cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 100 U/ml penicillin, 100 mg/ml streptomycin, 2 mM glutamine and 10% fetal bovine serum (FBS). Cells were