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Relaxation and guided imagery program in patients with breast cancer undergoing radiotherapy is not associated with neuroimmunomodulatory effects

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Abstract

Objective: Treatment of breast cancer is usually associated with significant psychological stress. In this study, we examined the effects of relaxation and visualization therapy (RVT) on psychological distress, cortisol levels, and immunological parameters of breast cancer patients undergoing radiotherapy. **Methods:** Participants were randomly assigned to either the experimental (n=20) who underwent group RVT for 24 consecutive days or control group (n=14) who were on radiotherapy only. Psychological scores (stress, anxiety, and depression) were measured by structured clinical interviews. Salivary cortisol was assessed along the day. Lymphocytes were isolated and cultured to measure T-cell proliferation and sensitivity to glucocorticoids (GCs). **Results:** RVT was effective to reduce stress, anxiety, and depression scores (all $P<.05$). However, cortisol levels as well as proliferation remained unchanged following RVT. Although T cells of experimental group were more sensitive to GCs than cells of controls at baseline, no changes were noted following RVT. Cortisol levels were positively correlated to anxiety and depression scores and inversely correlated to T-cell proliferation and sensitivity to GCs. **Conclusion:** We conclude that the psychological intervention was capable to attenuate the emotional distress presented during radiotherapy treatment. A longer RVT or worse psychological morbidity at baseline may be necessary to translate psychological into biological changes.

Keywords: Psychoneuroimmunology; Breast cancer; Relaxation and visualization; Lymphocyte proliferation; Glucocorticoids; Intervention studies

Introduction

Negative psychological states are frequently associated to the diagnosis and treatment of breast cancer. Stress-related changes in the immune system may be important for breast cancer patients. Data from many studies have suggested that chronic psychological stress can adversely affect immune function [1–3]. These results should be interpreted with caution, as causality has not been determined. This study was undertaken to evaluate the psychological, endocrine, and immunological effects of a relaxation and visualization therapy (RVT) in breast cancer patients undergoing radiotherapy.

The possibility for an enhancement of immune function through psychological intervention has generated considerable interest. There is significant evidence that stress management interventions may have positive psychological effects [4,5]. A variety of psychosocial interventions in cancer such as education, behavioral techniques, and individual and

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group therapy have all been shown to reduce anxiety and depression while enhancing active coping styles [6–8]. In fact, a meta-analysis of 15 studies showed a decrease in depression and anxiety regardless of cancer type and adjunctive psychological therapy used [9]. Cancer patients usually seek alternative supportive therapies able to help their clinical treatment. This may further strengthen their coping skills to the disease as well as making them participants in their treatment. This is the rationale of Simonton's theory [10] in which patients are truly committed to their treatment, improve their quality of life, increase survival, or even induce remission of the disease.

Stress leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis, increasing peripheral cortisol that is known to have immunosuppressive effects [1]. Cortisol hypersecretion may also result in depressed mood [11]. In addition, previous work showed that breast cancer is associated with increased cortisol levels both prior to and following treatment [7]. However, low cortisol levels have been found among recently diagnosed breast cancer patients with a history of depression or posttraumatic stress disorder (PTSD) [12]. It has been shown that breast cancer is associated with flatter circadian pattern of HPA axis function [13]. Flatter daytime slopes of cortisol have been associated with fatigue in breast cancer patients [14,15] and were predictive of earlier mortality with metastatic breast cancer [16], independent of other known prognostic factors. In addition, depression was associated to blunted stress reactivity in metastatic breast cancer [17]. Recent work suggested that flatter daytime cortisol slopes among metastatic breast cancer patients may be related to disrupted feedback inhibition of the HPA axis rather than hypersensitivity in response to stimulation [18]. Psychological interventions aimed to reduce psychological stress and cortisol levels [19,20] could lead to improved immune function and health. To date, few studies have addressed this cogent relationship in breast cancer. A randomized controlled relaxation intervention with patients with advanced breast cancer was associated with reduced cortisol levels in those patients with increased cortisol levels at the beginning of the intervention [7]. Increased lymphocyte counts and reduced evening cortisol levels have been observed in breast cancer patients following a 10-week RVT [21]. Recently, a randomized clinical trial assessed the psychological, behavioral, and immune changes after a stress management intervention in a large sample (n=227) of breast cancer patients [22]. The intervention was effective to reduce anxiety scores, improve perceived social support, and dietary habits as well as maintaining stable or increasing mitogen-induced T-cell proliferation [22].

The measurement of peripheral hormones may not be sufficient to finally determine the functional hormonal action in target tissues. Glucocorticoid (GC) immunomodulation is orchestrated by specific binding of GCs on intracellular steroid receptors: mineracorticoid (MR) and GC receptors (GR). Although MRs have higher affinity for circulating GCs than GRs, most (if not all) effects on the immune system are mediated via GRs [23]. The presence of these receptors indicates that the immune system is prepared for HPA axis activation and the subsequent elevation in endogenous GCs. It has been suggested that chronically elevated cortisol levels may produce a state of acquired steroid resistance enabling lymphocytes to respond with less intensity to GCs. This phenomenon has previously been observed during major depression [24,25] and chronic stress [3,26,27]. We hypothesized that psychological distress experienced by breast cancer patients would be associated with reduced lymphocyte sensitivity to GCs. To date, it is largely unknown whether stress management interventions are able to restore this impaired cellular response.

Here, we investigated if RVT is capable to attenuate psychological distress (stress, anxiety, and depression), lower salivary cortisol levels, and increase nonspecific lymphocyte proliferative responses. Finally, we investigated the lymphocyte sensitivity to GCs in vitro to explore the functional hormonal action in the immune system.

Methods

Study design

This study was undertaken in a repeated-measures design with two time points. Psychological, endocrine, and immunological data were obtained at baseline and after a 24-day intervention. Each intervention included a group consisted of up to four patients. Salivary samples were collected three times a day to assess cortisol levels. Peripheral blood for the immunological tests was drawn at the same time of the day.

Subjects

A total of 34 subjects with breast cancer (Stage I or II) undergoing radiotherapy were recruited from the Radiotherapy Service at São Lucas Hospital (Porto Alegre, Brazil) and randomly assigned into two groups: (i) 20 patients as experimental group and (ii) and 14 patients as control group. The radiotherapy sessions never exceeded 10 min of radiation exposure (average, 5–7 min). The control group did not participate in the RVT intervention or in any other type of additional intervention. All subjects completed the two assessments and had at least 2 weeks of chemotherapy washout. Demographic information including age, ethnicity, religion, education, marital status, and occupation status was obtained on a form created for this study. The study protocol was approved by both scientific and ethics committees (PUCRS, Porto Alegre, Brazil), and written informed consent was obtained from all subjects.

Exclusion criteria included presence of acute or chronic infections, heart disease, anorexia, anemia, leucopenia, clinical depression, PTSD, neurodegenerative disease, and use of GCs.