EFFECT OF AEROBIC EXERCISE ON CANCER PAIN IN METASTATIC SOLID TUMORS PATIENTS RECEIVING PALLIATIVE RADIOTHERAPY

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ABSTRACT

Purpose: The current study was conducted to evaluate the effect of aerobic exercise on cancer pain in patients with solid metastatic tumors receiving palliative radiotherapy. Methods: Thirty-six patients from both genders were included in this study. Their ages were ≥ 18 years. They were randomly divided into two groups equal in number (each 18 patients). Procedures: Group I (Study group) received the program of aerobic exercise using the bicycle ergometer (30 minute per session) 5 sessions per week for 2 weeks in parallel with the palliative radiotherapy and Group II (control group) received the palliative radiotherapy protocol only. Pain was assessed by the Visual Analogue Scale (VAS) and the blood Cortisol level was assessed before and after the program (2 weeks). Results: Post treatment comparison between both groups revealed a significant reduction in cortisol level and VAS of the study group in comparison with that of the control group. There was a significant reduction in cortisol level and VAS post-treatment compared with that of pretreatment in the study group (p > 0.001). The correlation between VAS and cortisol level was a positive and statistically significant correlation (r = 0.68, p = 0.0001). Conclusion: Short term moderate intensity aerobic exercise led to a significant decrease in cancer pain and blood cortisol (stress hormone) level in solid metastatic tumors patients receiving palliative radiotherapy.

Keywords: Aerobic exercise, Palliative radiotherapy, Solid metastatic tumors

I-INTRODUCTION

Cancer is a category of debilitating diseases whose incidence is steadily increasing across the world [1]. Solid tumors are abnormal tissue masses that are devoid of cysts or liquid areas. They can be benign or malignant [2]. Patients who suffer from solid tumors are particularly prone to metastases in the bones. Though any cancer can spread to the bone, the most common are advanced breast (70–80 %), prostate (70–80 %), thyroid (60 %), lung (10–50 %), and renal cancers (30 %). Other malignancies are also seeing an increase in bone metastases. Metastases commonly occur in the proximal femur, pelvis, vertebrae, and skull. but distal bone metastases are uncommon. Bone metastasis is a terrible disease that can negatively influence the lives of advanced cancer patients in a variety of ways [3].

Over the last decade, there has been a tremendous amount of research into metastatic occurrences in various malignancies [4]. Pain, tiredness, anxiety, depression, lack of appetite, decreased joint range of motion, exercise intolerance, and physical inactivity are all common side effects that cancer survivors experience after surgery, chemotherapy, and radiation treatment [5]. Cancer survivors’ quality of life is also harmed by these secondary effects of therapy [6]. Bone metastasis is observed in 70% of metastatic prostate and breast cancer patients, and
it is the third most frequent site of metastasis for a variety of solid tumors, including lung, breast, prostate, colorectal, thyroid, gynecologic, and melanoma. Regrettably, once cancer has expanded to bone, it is seldom treated and is accompanied with a variety of complications such as pain, fracture threat increase and hypercalcemia [7].

Pain is a common sign of cancer; 75% of cancer patients suffer pain during their illness, and approximately 50 % of that pain goes untreated. Cortisol levels rise when pain isn't alleviated [8]. For the relief of localized bone pain, radiation therapy (RT) is the treatment of choice. Radiation therapy is with high-energy x-rays are used in cancer therapy. Palliative therapy is provided as a treatment that aims to reduce the size of a malignancy, delay its progression, or alleviate cancer-related symptoms. Because it is not intended to treat cancer, lower doses of radiation can be safely applied without causing significant adverse effects to the patient [9].

Around 6 out of 10 individuals with cancer-induced bone pain are caused by bone metastases. Consequently, radiation treatment provides pain alleviation [8]. Palliative radiation therapy, typically in combination with opioids and co-analgesics, is a common therapeutic option for cancer-related bone pain. Unfortunately, not all patients who receive RT find pain alleviation. About a quarter of the patients claim complete pain relief, while 40–60 percent report partial pain relief. The average time it takes for pain response is 1 to 4 weeks [10].

Physical activity has been recommended as a non-pharmacologic strategy to help cancer patients cope with the physiologic and psychological side effects of treatments [11]. Physical exercise reduces pain by improving strength, flexibility, cardiorespiratory fitness, and quality of life while also reducing tiredness, duration of hospital stay, stress, anxiety, nausea, vomiting depression and sleep problems [12]. It also helps with treatment reactions, mood, body image, and body mass maintenance. Physical exercise training has also been used to assist healthy people to lower their cortisol levels. In major depressive disorders, physical activity induces a moderate decrease in cortisol levels (MDD). Individuals' cortisol levels are reduced by physical activity, depending on the type of exercise (aerobic exercise), weekly frequency (five times per week) and type of cortisol measurement [13]. Therefore, this study was conducted to evaluate the effect of short-term aerobic exercise on cancer pain in patients with solid tumors receiving palliative radiotherapy.

II- MATERIALS & METHODS

- **Design of the study**
  The study was designed as a prospective, randomized, double blind, pre and post test, controlled trial.

- **Subjects**
  Thirty-Six patients suffering from solid lesion pain (bone or soft tissue) due to (breast, prostate or lung) cancer metastasis and receiving palliative radiotherapy were enrolled in this study from the Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Cairo University. They were chosen under the following criteria: Both genders (males and females) were involved in this study, patients’ ages were ≥ 18 years, all patients had pathologically proven breast, prostate or lung cancer and had evidence of bone metastasis by bone scan, x-ray or computerized tomography (CT). All patients received a palliative radiation therapy program. All patients’ performance status was 0 -2 according to the world health organization (WHO) and the therapeutic intervention for all patients began in parallel with the palliative radiotherapy program. Patients excluded from the sample were those who had pathological fractures in long bones or corticosteroids therapy.

  Randomization was carried out for distribution into two groups of 18 patients each: Group A (study group) and Group B (control group) by a blinded and independent researcher. Group A (Study group): included (12 females, 6 males) receiving the program of aerobic exercise using the bicycle ergometer (30 minute per session) 5 sessions per week for 2 weeks in parallel with the palliative radiotherapy sessions. Group B (Control group): included (13 females, 5 males) receiving the palliative radiotherapy program only. They were all analyzed as no participants pulled out of
the study after being randomly assigned. Methods of assessment whether pre-treatment or post-treatment for both groups included VAS to measure pain and blood samples to measure the cortisol level.

The study’s protocol was reviewed and approved by the ethical committee of faculty of physical therapy Cairo University, Egypt [NO: P.T.REC/012/002172]. Each subject gave an informed consent before the study began.

- **Equipment:**
  - **Evaluation equipment:** Visual Analogue Scale, The rating of perceived exertion (The Borg Scale), GRANXIA pulse oximeter and Snibe Maglumi 1000 Fully Automated Chemiluminescence Immunoassay Analyzer (CLIA).
  - **Therapeutic equipment:** Magnetic bike Grand Fit 222C.

- **Evaluation procedures:**
  1. **The Visual Analogue Scale (VAS):**

    It was conducted before and after the palliative radiotherapy sessions to assess pain level. The VAS was explained to every patient. The VAS was used for assessing pain intensity. The scale is most commonly anchored by a “no pain” (score of 0) and “worst imaginable pain” (score of 10) [10-mm scale] [14].

  2. **The Borg Scale:**

    The rating of perceived exertion (RPE) was used in this study to measure the intensity of physical exercise and was therefore utilized as a work intensity indicator. It is a key component in the prescription of exercise training intensity for both healthy and special populations. The RPE score is considered reliable and valid, with a moderate to high correlation with respiratory parameters, heart rate (HR) and blood lactate in healthy individuals. A Borg RPE scale of 6 corresponds to a heart rate of 60 beats/min in a healthy adult. An exercise RPE scale of 8 represents 80 beats/min and so on. A moderate exercise RPE scale ranges between 12 &14 [15]

  3. **Cortisol measurement:**

    The blood samples were taken from both groups before and after two weeks of the experiment. Blood samples were withdrawn in the morning at 9 am. Each patient was well rested and seated for 5-10 minutes before blood collection. About 5 ml of venous blood was withdrawn on EDTA that was centrifuged at 1500 rpm for 10 minutes. Cortisol was quantified in plasma samples using the fully automated chemiluminescence immunoassay analyzer (CLIA) Maglumi1000, according to the manufacturer’s instructions.

- **Therapeutic procedures:**
  1. **The physical therapy program:**

    The physical therapy program of aerobic exercises was conducted to patients in study group (A). It started by a five minute “warming up” exercise on the bicycle ergometer in the form of a slow progression exercise to decrease the risk of hypotension, musculoskeletal injury and cardiovascular complications followed by an “active phase” for 10- 20 minutes at moderate intensity (12-14 on Borg scale) and finally a cooling down five-minute exercise with intensity and speed declination until reaching the resting heart rate [16].

  2. **The palliative Radiotherapy Technique:**

    All patients in both groups received palliative radiotherapy for bone or soft tissue lesions as a single fraction (7-8 gray), 20 gray over 5 fractions in a week or 30 gray over 10 fractions in 2 weeks on a linear accelerator [17].

- **Statistical analysis**

  All statistical analysis was conducted through the statistical package for social studies (SPSS) version 25 for windows (IBM SPSS, Chicago, IL, USA). For age comparison among groups, descriptive statistics and an unpaired t-test were used. The chi-squared test was used to compare gender and origin of bone metastasis distribution between groups. The Shapiro-Wilk test was used to ensure that all variables had a normal distribution. To determine group homogeneity, Levene's test for homogeneity of variances was used. To compare the study and control groups’ mean values of cortisol levels and VAS, an unpaired t-test was used. For each group, to compare before and after therapy,
a paired t-test was performed. The correlation between VAS and cortisol level was investigated using the Pearson correlation coefficient. For all statistical tests, the significance threshold was set at p < 0.05.

III- RESULTS

There were no significant differences between both groups as regards the mean age, sex and origin of bone metastasis distribution (p > 0.05). (Table 1).

Table 1. Comparison of subject characteristics between study and control group:

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.88 ± 17.7</td>
<td>55.44 ± 16.02</td>
<td>0.79</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>12 (67%)</td>
<td>13 (72%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Males</td>
<td>6 (33%)</td>
<td>5 (28%)</td>
<td></td>
</tr>
<tr>
<td>Origin of bone Mets, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>9 (50%)</td>
<td>11 (61.1%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Prostate</td>
<td>5 (27.8%)</td>
<td>5 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4 (22.2%)</td>
<td>2 (11.1%)</td>
<td></td>
</tr>
</tbody>
</table>

\( \bar{x} \), mean; p value, probability value; ; SD, standard deviation * significant.

- **Comparison within groups:**

There was a significant reduction in cortisol level and VAS post-treatment compared to that of pretreatment in the study group (p > 0.001). The percentage of decrease in cortisol level and VAS in the study group was 28.98 and 22.65% respectively. As regards the control group there was a major elevation in cortisol level (51.41%) and VAS (3.67%) post-treatment compared to that of pretreatment (p < 0.05) (Table 2).

- **Comparison between groups:**

As regards pre-treatment, there was an insignificant difference in cortisol levels or VAS between both groups (p > 0.05). Whenever the cortisol level and VAS of the study group were compared to that of the control group after treatment, the cortisol level and VAS of the study group were significantly decreased (p > 0.05). (Table 2, figure 1).

Table 2. Mean cortisol level and VAS pre and post-treatment of the study and control groups:

<table>
<thead>
<tr>
<th>Cortisol level (mcg/dL)</th>
<th>Study group</th>
<th>Control group</th>
<th>MD</th>
<th>t- value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>18.6 ± 6.12</td>
<td>16.63 ± 6.67</td>
<td>1.97</td>
<td>0.91</td>
<td>0.36</td>
</tr>
<tr>
<td>Post treatment</td>
<td>13.21 ± 4.67</td>
<td>25.18 ± 5.78</td>
<td>-11.97</td>
<td>-6.82</td>
<td>0.001*</td>
</tr>
<tr>
<td>MD</td>
<td>5.39</td>
<td>-8.55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of change</td>
<td>28.98</td>
<td>51.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t- value</td>
<td>6.32</td>
<td>-6.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = 0.001*</td>
<td>p = 0.001*</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>VAS</th>
<th>Study group</th>
<th>Control group</th>
<th>MD</th>
<th>t- value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>9.05 ± 0.87</td>
<td>9.27 ± 0.67</td>
<td>-0.22</td>
<td>-0.85</td>
<td>0.39</td>
</tr>
<tr>
<td>Post treatment</td>
<td>7 ± 1.08</td>
<td>9.61 ± 0.6</td>
<td>-2.61</td>
<td>-8.91</td>
<td>0.001*</td>
</tr>
<tr>
<td>MD</td>
<td>2.05</td>
<td>-0.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of change</td>
<td>22.65</td>
<td>3.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t- value</td>
<td>8.73</td>
<td>-2.38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = 0.001*</td>
<td>p = 0.02</td>
<td></td>
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</tbody>
</table>

SD, standard deviation; MD, mean difference; p-value, probability value; *, significant.
Analysis of the data showed a moderate positive significant correlation between VAS and cortisol level ($r = 0.68$, $p = 0.0001$). (Figure 1).

**Figure (1)**. Correlation between VAS and cortisol level.

**IV- DISCUSSION**

The solid metastatic tumors patients usually suffer from pain, depression, anxiety, sleep disturbances, stress, which severely affect their daily activities and negatively impact their quality of life [18]. There is no consensus in the literature on the optimal way to treat pain in cancer patients. Pain as an endpoint in these individuals is rarely studied in clinical trials [19]. The current study was performed to assess the effect of aerobic exercise with moderate intensity on cancer pain in solid metastatic tumors patients receiving palliative radiotherapy. In this study, a comparison between groups regarding post-treatment results revealed a significant decrease in cortisol levels and VAS of the study group compared to that of the control group. There was a significant decrease in cortisol levels and VAS post-treatment compared to those of pretreatment in the study group. Furthermore, there was a significant moderate positive correlation between VAS and cortisol level. In addition to reduction of pain, exercise also lowered the blood cortisol (stress hormone) level in the current study. This shows that physical activity can be a useful non-pharmacological treatment of metastatic solid tumors during and after palliative radiotherapy treatment and this agrees with a study conducted by Žychowska et al., 2017 [11].

The palliative radiotherapy program was conducted as the treatment of choice for the relief of localized bone pain. Palliative radiation therapy is a common treatment for cancer bone pain, typically in combination with opioids and co-analgesics, and physical exercise that has lately been included to improve outcomes [10].

The aims of palliative care are pain reduction, function preservation, and bone integrity preservation. Early intervention may be beneficial in preserving the quality of life (QOL) for 60% of patients while palliative radiation gives pain relief in a median of 2-3 weeks [20].

The results of this study can be attributed to the fact that moderate intensity aerobic exercise alleviates the pain which consequently has an effect on cortisol (stress hormone) level and its value positively correlates with QOL as mentioned by [21].

The results of the current study agree with Žychowska et al., 2017 [11] who stated that physical activity has been recommended as a non-pharmaceutical intervention to help cancer patients deal with the physiologic and psychological side effects of treatments. Furthermore, the benefits of exercise training in cancer patients were confirmed in previous researches that included improving QOL (Mishra et al., 2012 [22]; Fong et al., 2012[23]; Strasser et al., 2013[24]; Hojan et al., 2017[12] and Yang et al., 2020[25]) [19], and positively affecting physical function, pain, fatigue, stress and QOL in patients with cancer undergoing surgery, chemotherapy or radiotherapy or both [21].

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The results of Beserra et al., 2018 [13] came in accordance with the current results as they reported significant moderate reduction in cortisol levels with a moderate intensity aerobic exercise program while radiation therapy (RT) was associated with elevation in stress levels [26]. Chronic stress can cause a variety of hypothalamic-pituitary-adrenal axis (HPA) abnormalities and cortisol secretion changes in the adrenal cortex. Increased chronic pain caused by tumors or surgery, therapies (chemo and irradiation) cause stress and the release of different stress hormones that may impact the success of treatment, particularly radiation therapy (RT) in cancer patients. Increasing the effectiveness of radiotherapy by reducing chronic stress might be very beneficial [27].

V- CONCLUSION

Short term moderate intensity aerobic exercise led to a significant relief of cancer pain and reduction in blood cortisol (stress hormone) level in solid metastatic tumors patients receiving palliative radiotherapy.

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