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Effects of Illite Thermotherapy on NK Cells, Serotonin, and BDNF in Cancer Survivors

Hyun-Jun Kim[1], Hyoung-Kil Kang[2], Sung-Hoon Kim[3], Wook Song[4], Yu-Kyoum Kim[5], Won-Sik Bae[*6]

[1]Professor, Dept. of Physical Education, Kyungnam University, 7, Kyungnamdaehak-ro, Masanhappo-gu, Changwon, Kyungsangnam-do, Korea

[2]Professor, Dept. of Physical Education, Kyungnam University, 7, Kyungnamdaehak-ro, Masanhappo-gu, Changwon, Kyungsangnam-do, Korea

[3]Ph.D. student, Dept. of Physical Education, Kyungnam University, 7, Kyungnamdaehak-ro, Masanhappo-gu, Changwon, Kyungsangnam-do, Korea

[4]Professor, Dept. of Physical Education, Seoul National University, 1, Gwanak-ro, Gwanak-gu, Seoul, Korea

[5]Professor, Dept. of Physical Education, Seoul National University, 1, Gwanak-ro, Gwanak-gu, Seoul, Korea

[6]Professor, Dept. of Physical Therapy, Kyungnam College of Information & Technology, 45, Jurye-Ro, Sasang-gu, Busan, Korea

Abstract

The purpose of this study is to obtain empirical evidence for the effects of illite thermotherapy on the levels of NK cells, serotonin, and BDNF among cancer survivors. 10 subjects were selected in this study based on the results calculated using G*Power 3.1 with power (type 1-2 error [β]) = .85 and significance level (α) = .05. Ten women aged 45.7±10.91 years residing in G city, Korea, were enrolled in the study. All participants had experienced cancer. During the study period, all participants used an illite hot water mat from six to eight hours per day for four weeks while sleeping. The paired t-test was used to compare differences in NK cells, serotonin, and BDNF levels between week 0 and week 4, between week 4 and week 6, and between week 6 and week 10. As a result of a 10-week experiment of using an Illight mat and a hot-water mat on 10 cancer patients for 10 weeks, the changes in body composition showed significant differences in body weight, BMI, body fat mass, and body fat percentage. The number of NK cells was significantly increased after two weeks of washout ($p<.05$). Serotonin levels decreased significantly after two weeks of washout ($p<.01$). BDNF decreased significantly after ten weeks of thermotherapy ($p<.01$).

Conclusionally, based on the findings of the present study, a follow-up study with an extended period of the use of an illite hot water mat and a larger sample size is necessary.

Keywords: BDNF, Body composition, Cancer, Illite thermotherapy, NK cells, Serotonin

1. Introduction

Although humans began to use clay for healing in the Aristotelian era (384–322 BC)[1], researchers have only recently become interested in understanding the role of clay in promoting human health. Clay may soothe infected gastrointestinal lining[2] and absorb toxins from skin[3]. In East Africa, the use of clay minerals as a therapeutic treatment is common[4], and researchers have reported that clay has antibacterial properties[5]. Clay can also provide the body with heat to stimulate blood circulation and increase body temperature to stimulate circulation in alternative medicine treatments[6].

Clay minerals for healing include smectites, palygorskite, mica, kaolinite, and talc. Of these clay minerals, lithium-mica is known to induce sleep and detoxicate the body. Illite, a type of lithium-mica that presents in extremely fine-grained greenish-gray masses, is popular in Korea for use in lessening many physical symptoms. Koreans believe that illite is effective in increasing core body temperature, strengthening the immune system, and enhancing emotional status. Hence, illite is added into a variety of products, such as necklaces, wristbands, soap, massage chairs, abdominal bandages, mask packs, water bottles, and hot water mats. However, the effectiveness of illite clay products has not been empirically examined. Thus, the purpose of this study is to obtain empirical evidence for the effects of

illite hot water mats on the immune systems and emotional status of cancer survivors.

In this study, cancer survivors were selected as study participants. In 2014, more than one million cancer survivors lived in Korea[7]. Because of this issue, the Korean government is seeking clinical and political strategies for cancer survivors. [8] studied survivorship in cancer patients, which was the origin of the term cancer survivors. [8] proposed that cancer patients experience three stages: acute survival, extended survival, and permanent survival. In the stage of acute survival, cancer patients undergo intense anticancer treatments; in the stage of extended survival, cancer patients are monitored and observed without medical treatment; and in the stage of permanent survival, a successful cure or a very low risk of recurrence is expected, and cancer progression is halted. The participants in this study were in the extended survival stage. They were in a nursing home, and although many suffered from psychological and physiological side effects of anticancer treatments, they had a strong interest in their health.

This study measured levels of natural killer (NK) cells in cancer survivors to assess whether illite thermotherapy was the best option for relieving pain caused by muscle spasms or cramps that affected their immune systems. NK cells, which are innate lymphoid cells, are effective in eliminating malignantly transformed and virus-infected target cells[9], and they participate in the coordination of immunity[10]. In particular, NK cells contribute to cancer immunoediting[11], and they are closely associated with significant immunoevasion in cancer progression and in tumor cell surveillance[10,12]. Cancer patients have dysfunctional or deficient NK cells[13], and increases in cancer risk are predicted by decreased NK cell function[14]. For these reasons, this study aims to assess the levels of NK cells among cancer survivors.

This study also measured levels of serotonin to understand the emotional status of cancer survivors. Serotonin, as a biogenic monoamine, functions as a neurotransmitter in the central nervous system (CNS)[15]. Serotonin has been linked to brain development, thermoregulation, Parkinson's disease, hallucinations, schizophrenia, cognition, pain, violent behavior, and motor function. Serotonin has also been found to relate to depression, sexual drive, bulimia, addiction, chronic stress, mood, fear, and anxiety. It is also a well-known contributor to feelings of happiness and well-being[16]. Thus, serotonin levels can represent emotions. Moreover, serotonin is related to cancer, as serotonin synthesis can prevent cancer cell growth[17]. Hence, because serotonin could be an important indicator of the health and emotional status of cancer survivors, this study measured the levels of serotonin in cancer survivors.

Lastly, this study measured the levels of the brain-derived neurotrophic factor (BDNF) in cancer survivors. BDNF plays a vital role in modulating the nervous system[18] and helps to support the survival of existing neurons and the growth of new neurons and synapses[19]. BDNF is closely associated with the pathophysiology of symptoms[20], and it has been found to be important in learning, higher thinking, and long-term memory[21]. Degrees of clinical impairment were found to be correlated to reduced BDNF, and increased BDNF expression was positively related to low levels of depression[22]. Cancer survivors who endured chemotherapy or radiation therapy reported fatigue and depression[23]. Because BDNF levels are negatively related to depression, this study attempts to understand the effects of illite thermotherapy on BDNF levels in a cohort of cancer survivors.

The purpose of this study is to obtain empirical evidence for the effects of illite thermotherapy on the levels of NK cells, serotonin, and BDNF among cancer survivors. Based on this purpose, the following research questions were formulated: to determine the effects of illite thermotherapy on body composition and improvement in immune function.

2. Materials and Methods

2.1. *Participants*

This study was approved by the Institutional Review Board of Kyungnam University (1040460-A-2018-026), and it was performed in accordance with the principles stated in the Declaration of Helsinki. A power analysis was conducted using G*Power 3.1. To obtain results of a two-tailed test at the 0.05 level and a power of 85%, a total sample size of 10 participants was needed to detect a desirable effect size of 0.5. Written informed consent was obtained from all participants before their enrolment in the study. Ten women aged 45.7±10.91 years residing in G city, Korea, were enrolled in the study. All participants had experienced cancer. They had not taken any supplements or medications, including antidiabetic drugs, antihypertensive drugs, or cognitive-enhancing drugs during the previous four weeks. In addition, they had no experience in using a hot water mat in the last eight weeks.

2.2. *Intervention*

During the study period, all participants used an illite hot water mat from six to eight hours per day for four weeks while sleeping. The temperature of the illite hot water mat was set from 35 to 40 ºC. The illite hot water mat was placed on the bed in the living room where the participants lived, and it was used every day. Four weeks later, the participants stopped using the illite hot water mat for two weeks. Thereafter, they used the hot water mat following the same protocol for four weeks.

2.3. *Measurements*

All participants' blood samples were collected at four time points, immediately before they started to use the illite hot water mat (week 0) and immediately after (week 4). Two weeks later (week 6), they finished using the illite hot water mat (week 10).

To measure the body composition of the subjects, InLab S50, which measures height with an ultrasonic sensor, and InBody 370 (Biospace, Co. Korea), which measures body weight, body mass index (BMI), body fat mass, body fat percentage, and muscle mass, were used. The measurement principle applied was the four-electrode method, which includes eight contact electrodes at a frequency range of 20,100 kHz. For the measurement method, bioelectrical impedance analysis (BIA) was used, in which the subject took an upright position, and then the start button was pressed to turn on the microprocessor to measure the entire body and individual body parts (i.e., left arm, right arm, torso, left leg, and right leg).

About 5 mL of blood was collected from the antecubital vein after the participant had fasted for more than 10 hours. The sample was mixed thoroughly in an anticoagulant (EDTA WB)-containing tube and then stored in the refrigerator before it was sent to company G for analysis. The analysis items were NK cells, serotonin, and BDNF.

In the blood analysis, NK cells were stained by double fluorescence using a combination of monocyte antibodies to determine the activities of the cells (CD16+CD56) in an EDTA tube, followed by flow cytometry (FC 500, USA). The serotonin analysis was performed using the Human Serotonin ELISA kit (Catalog #LF-EK5005, Ab frontier, Inc.), and BDNF was analyzed using the Human BDNF ELISA kit (Catalog #LF-EK5005, AbFrontier, Inc.).

2.4. *Data analysis*

The results of the Shapiro-Wilk test verified that all parameters showed normal distribution. Parametric variables that were normally distributed were expressed as mean ± SDs, while changes in parameters that were not normally distributed were expressed as median and 95% CIs. The first paired t-test was used to compare differences in body composition, NK cells, serotonin, and BDNF levels between week 0 and week 4, between week 4 and week 6, and between week 6 and week 10. Statistical analyses were performed using the Statistical Package for Social Sciences ver. 18.0 for

Windows (SPSS, Inc., Chicago, USA). Statistical significance was accepted at p values < 0.05.

3. Results and Discussion

3.1. *Changes in body composition*

Table 1 shows changes in body composition by the four-week illite thermotherapy and the four-week thermotherapy in 10 cancer patients.

Table 1. Changes in Body Composition

Variables	o week (A)	4 weeks (B)	6 weeks (C)	10 weeks (D)	A-B	B-C	C-D
					t	*t*	*t*
Weight (kg)	59.52 ±4.04	57.52 ±3.97	59.16 ±4.69	59.38 ±4.16	3.581**	-3.018*	-.576
BMI (kg/m2)	22.75 ±1.80	21.88 ±1.86	22.84 ±2.32	22.86 ±2.14	4.356**	-2.338*	-.073
Fat mass (kg)	19.28 ±4.15	16.7 ±4.04	18.50 ±4.25	18.56 ±4.47	5.867***	-4.517**	-.214
Fat percentage (%)	32.16 ±5.45	28.69 ±5.80	31.06 ±5.68	31.01 ±6.19	7.183***	-3.726**	.137
Muscle mass (kg)	21.73 ±1.32	22.07 ±1.53	22.05 ±1.98	22.13 ±1.81	-2.279*	.064	-.423

Value: Mean±Standard deviation, BMI: body mass index, A-B: Comparison of before and after using illite warm water mat for 4 weeks using paired t-test, B-C: Comparison of before and after washout for 2 weeks using paired t-test, C-D: Comparison of before and after using warm water mat for 4 weeks using paired t-test, *: p<.05, **: p<.01, ***: p<.001

These are the results of analyzing changes in body weight, BMI, and body fat percentage after the four-week illite thermotherapy, the two-week washout, and the four-week thermotherapy over a period of 10 weeks.

The results showed that body weight and BMI decreased significantly after four weeks of illite thermotherapy (p<.01) but increased significantly after two weeks of washout (p<.05). Body fat mass and body fat percentage decreased significantly after four weeks of the illite thermotherapy (p<.001), but increased significantly after two weeks of wash out (p<.01). Muscle mass increased significantly after four weeks of illite thermotherapy (p<.001).

In their review of cases of cancer regression and prolonged lifespan in cancer patients, [24] found a prolonged lifespan in cancer patients who had suffered fever-causing diseases. Other studies showed that the function of macrophages was improved, and cytokine expression was enhanced in the fever-temperature range, which led to the improved protection of the host. In addition, a study on cellular protein levels reported that TRPM2 protein, a Ca^{2+} permeable cation channel, which is known to be expressed on the surfaces of not only macrophages but also of various immune cell types, is activated by elevated temperatures, which leads to the increased phagocytosis of macrophages[25]. Because these studies have demonstrated that body temperature plays an important role in enhancing

immunity, various treatment methods using thermotherapeutic devices [26] have been suggested. Therefore, the present study aimed to analyze the effects of an illite hot water mat and a conventional hot water mat on the body composition and immune function of cancer survivors after the four-week application of each hot mat in the same subject.

In this study, changes in body composition were analyzed after illite thermotherapy and conventional thermotherapy. After the illite thermotherapy, significant decreases in body weight, BMI, body fat, and body fat percentage and a significant increase in muscle mass were found, but no significant differences were found after conventional thermotherapy.

The results of this study are consistent with the results of a previous study conducted by [27], which reported decreases in BMI, body fat, and body fat percentage and an increase in muscle mass in middle-aged women after eight weeks of crystal thermotherapy.

These results are believed to have been caused by the elevated body temperature in thermotherapy, which increases the metabolic rate, that is, the oxidation rate, and energy consumption[28], subsequently leading to the breakdown of body fat. In particular, illite, which is a white or yellow, fine-grained clay mineral (particle size ≤ 2~4 ㎛) consisting of Si, Mg, H_2O contained in sedimentary rocks, is likely to promote the breakdown of body fat through increasing metabolism and blood circulation[29], which causes positive changes in body composition. In the present study, compared with positive changes in body composition after illite thermotherapy, there was no significant difference in body composition after conventional thermotherapy in the same subject. This result indicates that the application of an illite hot water mat is effective in reducing body weight, BMI, body fat mass, and body fat percentage as well as increasing muscle mass.

3.2. *Changes in NK cell, serotonin, and BDNF levels*

Table 2 shows changes in NK cell, serotonin, and BDNF levels after the four-week illite thermotherapy and the four-week thermotherapy in 10 cancer patients.

Table 2. Changes in NK Cell, Serotonin, and BDNF Levels

Variables	o week (A)	4 weeks (B)	6 weeks (C)	10 weeks (D)	A-B	B-C	C-D
					t	*t*	*t*
NK cell (pg/ml)	271.15 ±434.89	197.86 ±494.54	311.32 ±467.82	179.88 ±267.7	.398	-2.301*	.757
Serotonin (ng/ml)	117.23 ±21.15	132.04 ±19.47	104.60 ±21.75	108.64 ±20.5	-1.835	3.440**	.465
BDNF (ng/ml)	2460.74 ±333.21	2516.17 ±287.22	2474.76 ±232.98	2263.37 ±240.94	-.460	.491	2.582*

Value: Mean±Standard deviation, BDNF: Brain-derived neurotrophic factor, A-B: Comparison of before and after using illite warm water mat for 4 weeks using paired t-test, B-C: Comparison of before and after washout for 2 weeks using paired t-test, C-D: Comparison of before and after using warm water mat for 4 weeks using paired t-test, *: p<.05, **: p<.01, ***: p<.001

These are the results of the analyses of changes in NK cell, serotonin, and BDNF levels after the four-week illite thermotherapy, two-week washout, and four-week thermotherapy over a period of 10

weeks.

The number of NK cells was significantly increased after two weeks of washout ($p<.05$). Serotonin levels decreased significantly after two weeks of washout ($p<.01$). BDNF decreased significantly after four weeks of thermotherapy ($p<.01$).

Natural or intrinsic killer (NK) cells, which are found in the spleen, liver, and lungs, recognize and destroy a wide range of tumor cells, abnormal cells, and virus-infected cells, thereby playing an important role in immune function[9]. In particular, NK cells contribute to cancer suppression[11], and they are closely associated with significant immunity enhancement related to cancer progression and tumor cell surveillance[10]. Cancer patients have been found to have dysfunctional or deficient NK cells[13], and increased cancer risk may be predicted by a decrease in NK cell function[14].

In this study, changes in NK cells were analyzed after a four-week illite thermotherapy and a four-week conventional thermotherapy. Significant changes in NK cells were found four to six weeks (i.e., washout) after the illite thermotherapy (i.e., washout). A previous study conducted at Seoul Central Hospital demonstrated that in a high-temperature tumor cell experiment, of nine tumor cell types tested, except one tumor cell type, all showed a tumor necrosis effect after a heat treatment (43 °C), demonstrating that thermotherapy has a tumor necrosis effect. Considering that in the present study, significant changes were observed after the four-week illite thermotherapy and after six weeks following the two-week washout period, an experimental period of at least six weeks was required to confirm the effects of illite thermotherapy on NK cells in cancer survivors and that a resting period of two weeks was also needed following the four-week treatment. In future studies, it will be necessary to extend the treatment period of illite thermotherapy and to monitor the trend in changes in NK cell levels after the end of treatment.

Serotonin is also associated with fatigue, depression, libido, bulimia, addiction, chronic stress, mood, fear, and anxiety[16]. In particular, an increase in serotonin was found in cancer patients with chronic fatigue syndrome, and a relationship between cancer-related fatigue and serotonin was reported [30]. In addition, tissue damage due to surgery and various interventions used as anticancer therapy, such as chemotherapy and radiotherapy, induced the expression of transcription factors of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and promoted the production of cytokines, such as IL-1, IL-6, INF-γ; and TNF-α[31]. Increases in TNF-α and IL-1 promoted the expressions and activities of serotonin and noradrenaline reuptake transporters[32].

In this study, changes in serotonin levels were analyzed after four weeks of illite thermotherapy and four weeks of conventional thermotherapy. A significant decrease in serotonin levels was found four to six weeks (washout) after the illite thermotherapy. This result is similar to that in a previous study on alternative therapies, which reported decreases in serotonin receptors (HTR1A, HTR2C, HTR6) and serotonin transporters (SERT) after aroma therapy[33]. Although there were psychological and physiological differences in the results of aroma therapy and thermotherapy for fatigue, the reduction in serotonin through improvement of fatigue was consistent. The results of the reduction of serotonin during the washout period were believed to be caused by illite's cytokine suppressive effects through its various activities, such as cation exchange promotion, toxin removal, waste absorption, inflammation treatment through antibacterial action, antioxidant action, and the promotion of metabolism and blood circulation[29], which suppressed the secretion of serotonin. However, the finding that this significant decrease occurred after six weeks during the washout period, not immediately after the illite mat was used, indicates that an experimental period of more than four weeks is necessary to measure the efficacy of illite mats. Therefore, a study of illite mats over an extended application period is proposed.

BDNF plays an important role in regulating the nervous system[18] and helps support the survival of existing neurons and the growth of new neurons and synapses[19]. Elevated BDNF expression has been positively associated with low levels of depression[22]. Cancer survivors who have endured chemotherapy or radiation therapy showed fatigue and depression, and a negative correlation was found between BDNF levels and depression[23]. Cytokines such as TNF-α and IL-1 increase the secretion of the corticotropin-releasing hormone (CRH), which can cause the behavioral changes observed in patients with depression[34]. In addition, cytokines lower levels of neural growth factors, such as BDNF, which plays a major role in neurogenesis.

In this study, changes in BDNF were analyzed after four weeks of illite thermotherapy and four weeks of conventional thermotherapy. No significant difference was found between the two therapies, although an increasing trend was observed after the illite thermotherapy. This increasing trend is believed to result from the mineral characteristics of illite, which contains significant amounts of Si, Mg, and H_2O, but less K, which is an interlayer ion[35]. This property of illite is believed to be related to the increasing trend toward BDNF through its activities, such as toxin removal, waste absorption, and the suppression of inflammation mediated by antibacterial action[29].

4. Conclusion & recommendation

4.1. *Conclusion*

This study was conducted to analyze changes in body composition, NK cells, serotonin, and BDNF in cancer survivors after four weeks of illite thermotherapy, a two-week washout period, and four weeks of conventional thermotherapy-a total of 10 weeks. The study aimed to determine the effects of illite thermotherapy on body composition and improvement in immune function. The conclusions are as follows:

1. After four weeks of illite thermotherapy, significant decreases in body weight, BMI, body fat, and body fat percentage and a significant increase in muscle mass were observed.
2. NK cells significantly increased after the two-week washout period.
3. Serotonin significantly decreased after the two-week washout period.
4. BDNF showed an increasing tendency after four weeks of illite thermotherapy, but it significantly decreased after four weeks of conventional thermotherapy.

Overall, the results of this study demonstrated that the use of an illite hot water mat for four weeks had positive effects on the weight, BMI, body fat mass, body fat percentage, and muscle mass of the cancer survivors, whereas the use of a conventional hot water mat in the same subject for four weeks did not cause any significant changes in any body composition item. These results indicate that the illite hot water mat was more effective than the conventional hot water mat in improving body composition in cancer survivors.

4.2. *Recommendation*

There were significant differences in NK cells and serotonin after six weeks of illite thermotherapy, which suggests that an experiment period of at least six weeks of illite thermotherapy is required to measure the effects of immunity improvement by the use of an illite hot water mat. Based on the findings of the present study, a follow-up study with an extended period of the use of an illite hot water mat and a larger sample size is necessary.

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