

## ORIGINAL RESEARCH



# Modulation of the human immune status by spinal thermal massage: a non-randomized controlled study

Ka-Eun Kim<sup>1</sup>, Na-Ri Shin<sup>1</sup>, Soon-Hi Park<sup>1</sup>, Sang-Yun Nam<sup>1</sup>, Yong-Soon Yoon<sup>2</sup>, Soon-Kwon Park<sup>3</sup>, Jeong-Sook Park<sup>4</sup>, Il-Young Cho<sup>1,\*</sup>

<sup>1</sup>College of Medical Sciences, Jeonju University, 54896 Jeonju, Republic of Korea

<sup>2</sup>Department of Rehabilitation Medicine, Presbyterian (Jesus) Medical Center, 54987 Jeonju, Republic of Korea

<sup>3</sup>College of Social Sciences, Jeonju University, 54896 Jeonju, Republic of Korea

<sup>4</sup>Department of Nursing, Nambu University, 62271 Gwangju, Republic of Korea

**\*Correspondence**

[chirotrust@jj.ac.kr](mailto:chirotrust@jj.ac.kr)  
(Il-Young Cho)

**Abstract**

Thermal and massage therapies have long been used to control pain. Although spinal thermal massage (STM) has been used worldwide, its effectiveness has not been proven in a controlled clinical study. We here conducted a non-randomized controlled trial to assess the pain-relieving and immunomodulatory effects of STM in old-aged patients experiencing pain or disability. The experimental group was treated with STM five times a week for 8 weeks and rehabilitative regular care (RRC). The control group was treated with only RRC. Pain and immunological parameters were tested before treatment and after 4 and 8 weeks of treatment. The scores of three pain parameters were lowered by STM, and the differences between the groups were statistically significant at the two time points ( $p < 0.01$ ). Quality of life determined using the 3-level EuroQol five-dimensional questionnaire scores was significantly higher in patients in the experimental group than those in the control group. Effect sizes (ES) were in the range of medium to large in the pain-related measures (0.54–1.22). The total leukocyte counts and the proportions of lymphocytes and subsets were not significantly different between the groups, whereas the proportions of monocytes and natural killer (NK) cells were higher in the experimental group than in the control group after 8 weeks ( $p < 0.05$ ). The production of interleukin (IL)-4 and interferon  $\gamma$  in T cells was not significantly different between the groups, whereas the production of IL-2 was high in the control group. However, there was a significant increase in IFN- $\gamma$  production by NK cells in the experimental group (at 4 weeks,  $p < 0.05$ ). ES were medium in the immunological measures (0.53–0.68). No significant difference was observed in the production of proinflammatory cytokines, IL-1 $\beta$ , tumor necrosis factor  $\alpha$ , or IL-6 between the groups. In conclusion, STM treatment has a positive effect on subjective pain and quality of life. It also enhanced NK cell proportion and activity, suggesting that STM may be beneficial in the prevention of viral diseases and cancer in old-aged people.

**Keywords**

Spinal thermal massage; Pain; Immune modulation; Natural killer cell; Cytokine

## 1. Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage and can be described in terms of such damage [1]. Furthermore, pain is a complex, multi-dimensional sensation that is difficult to describe because it arises from traumatic or pathophysiological causes and is influenced by psychological, emotional, and cognitive factors [2].

In addition to conventional therapies such as pharmacologic treatment, physical therapy (including exercise, massage, and thermal and electrical treatments) has been used to treat chronic pain [3, 4]. Massage is a nonpharmacological therapy that is a part of complementary and integrative medicine, and it has been used for pain management; its mechanism of action

is becoming increasingly clear [5]. Korea [6, 7] and several European countries [8, 9] have developed various devices for automated massage that can be used in combination with other physical therapies aimed at pain or stress management.

It has been well documented that these painful experiences are powerful stressors, and these stresses trigger neuroendocrine activities that can lead to the suppression of some immune functions [10, 11]. Conversely, pain relief may restore impaired immunity. Pain management may also indirectly affect immune function by facilitating physical exercise, particularly in the elderly and patients with pain. It has been reported that exercise enhances T cell, B cell, and natural killer (NK) cell functions by altering the secretion of cytokines and hormones [12].

Additionally, strong associations between pain and tran-

scriptional or epigenetic changes in the blood have been reported [13]. A recent study using a rat model of spared nerve injury showed that DNA methylation changes are associated with neuropathic pain in peripheral T cells. These changes showed a striking overlap with cells in the prefrontal cortex [14]. Inflammation is an essential component of several painful syndromes, including arthritis, inflammatory back pain, traumatic pain, and postoperative pain [15]. Leukocytes are the source of hyperalgesic and analgesic mediators [16]; therefore, immune modulation may result in pain relief. This hypothesis has been strongly supported by several clinical studies, showing that physical therapeutic agents may influence pain by resolving inflammation [17].

These results strongly suggest that immune modulation may be involved in the reduction of pain. Previous studies have shown that spinal thermal massage (STM) can relax the autonomic nervous system [6] through physical and physiological changes [7]. However, to our knowledge, only one non-controlled pilot study with 10 healthy subjects has addressed the immunomodulatory effect of STM [18]. Our controlled study focused on old-aged individuals and patients with pain who are the main recipients of this therapy and who have been well documented to have a variety of immune impairments [19]. In the current study, we aimed to confirm the effect of STM on pain management and assess whether it influences the immunological function of patients experiencing pain and immunocompromised patients.

## 2. Methods

### 2.1 Participants

One hundred and forty individuals above 60 years of age with a disability caused by damage to the central nervous system for more than 6 months were recruited for the study. All recruited patients had symptoms of neck, shoulder, buttock, or knee pain and back muscle pain for more than 3 months. As the medical history record of each patient is important, patients with a stroke and with similar histories were included, and these patients were expected to have a reduced immune function because they cannot maintain normal activities for a long time due to central nervous system damage for more than 6 months. Participants with an immunological disease, a cardiac pacemaker, a transplanted electrical device, a malignant tumor, a spinal cord infection, thrombosis, a suspected skin disease, skin irritation, a vertebral deformity, scoliosis with Cobb's angle of 20° or more, a history of vertebral fractures due to osteoporosis, severe osteoporosis, vertebral fractures, myopathies, and back syndrome after spinal surgery were excluded from the study. Therefore, 130 participants were enrolled after the exclusions. Of the 130 participants, 65 were assigned to the control group receiving rehabilitative regular care (RRC) and 65 were assigned to the experimental group receiving STM and RRC. RRC mainly consists of occupational therapy performed by occupational therapists to improve upper extremity and daily life functions, and physical and occupational therapies consisting of balance and gait training and gait posture to improve lower extremity functions. It was not associated with the improvement in the immune function and it was

ethically necessary. During the 1-week adaptation process, four participants were excluded from the experimental group. During treatment, 4 participants from the control group and 6 from the experimental group were excluded, and a total of 116 participants completed the treatments. However, 57 blood samples were used for laboratory calibration to establish assay conditions for 15 immunological measurements, such as appropriate cell types, dilution rate with medium for whole blood culture, period of culture, concentration of stimulants, and dilution rate of samples for enzyme-linked immuno-sorbent assay. Finally, data derived of 29 control subjects (14 males and 15 females) and 30 experimental subjects (20 males and 10 females) were analyzed (Fig. 1). The mean duration of pain ( $\pm$  standard error [SE]) was 28.10 months (SE,  $\pm$  28.97 months) for the control group and 15.70 months (SE,  $\pm$  16.71 months) for the experimental group.

Written informed consent was obtained from all subjects before the study. This study adhered to the principles and recommendations of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board at the Presbyterian Medical Center (IRB no. 2017-06-022).

### 2.2 STM treatment

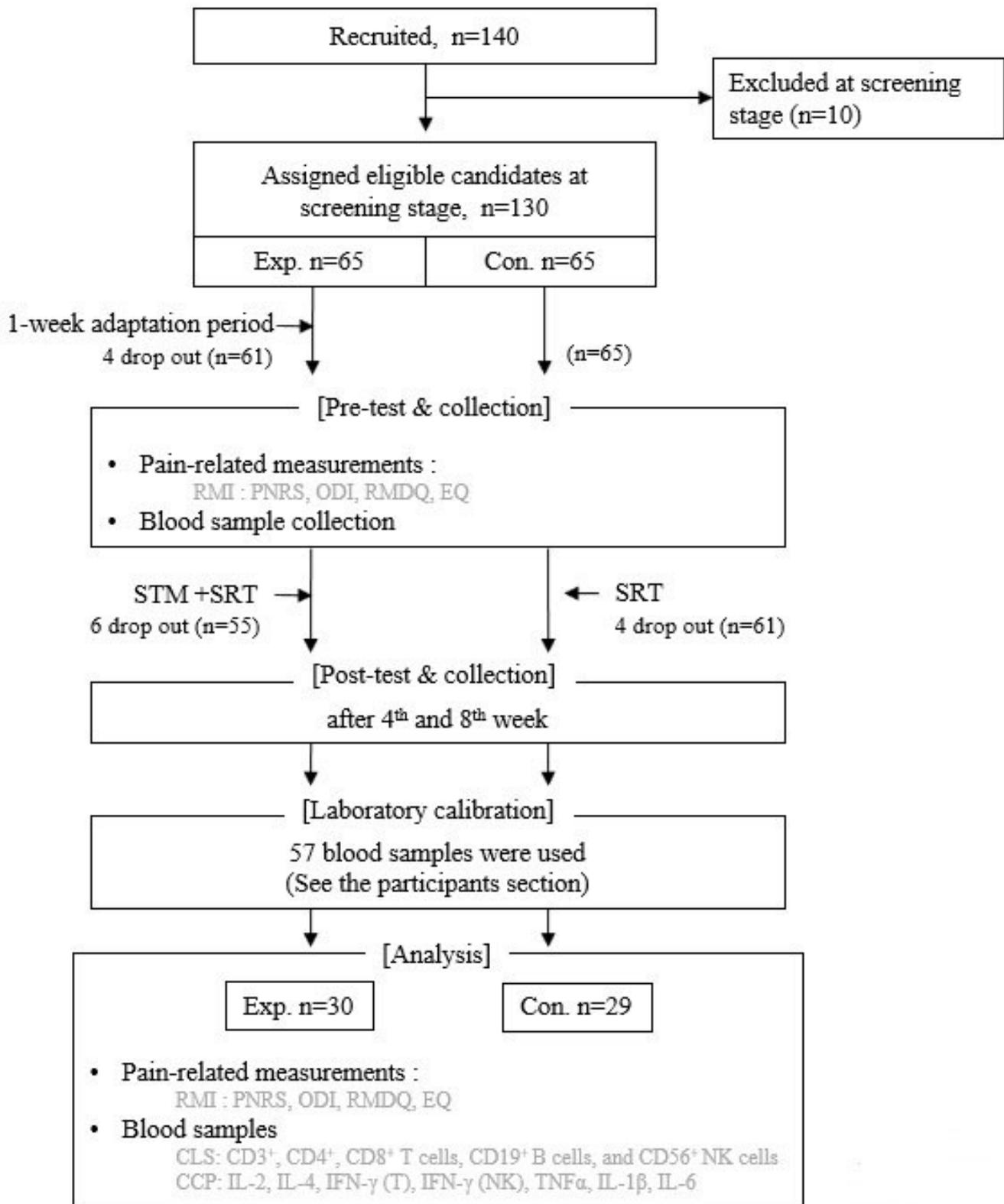
This study was conducted using a personal thermal device for relieving muscle pain (CGM MB-1401; Ceragem Co., Ltd., Cheonan, Korea), an instrument approved by the Food and Drug Administration of Korea and the United States as a personal thermal device for relieving muscle pain. The STM device provides a 36.5-min preprogrammed chiropractic massage sequence. During this sequence, a roller massages the muscles along the spine by moving cranially, caudally, and vertically for paraspinal massage and applies segmental acupressure at the basic strength presented in the program algorithm (Fig. 2). For thermal massage, heat is added to the program using a heating source inside the roller that can be set at 30 °C–60 °C. However, as the temperature suggested for the induction of immune response in previous studies related to hyperthermia treatment is 39 °C–41 °C [20], it was set to 43 °C considering the clothes the users were wearing. A trial session allowed participants to become familiar with the massage device.

### 2.3 Study design

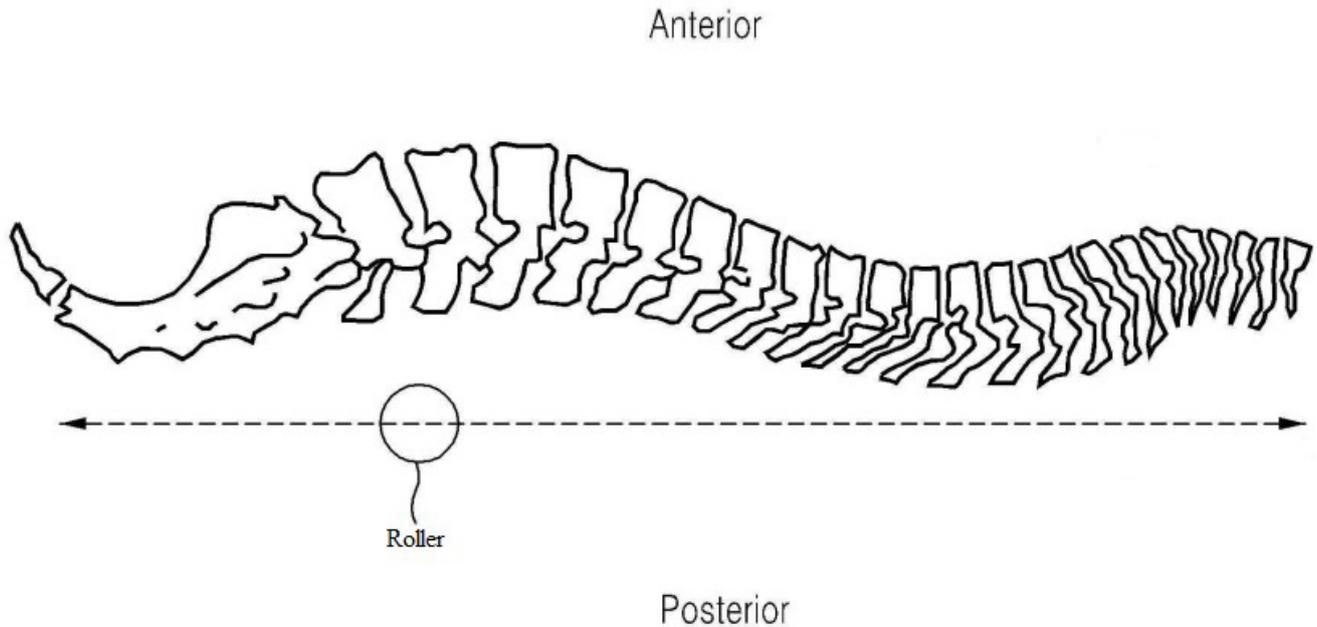
Data were collected and blood was drawn at the following three time points: before the massage, 4 weeks after the massage, and 8 weeks after the massage. Therefore, we conducted a non-randomized controlled study with repeated measures.

### 2.4 Rehabilitative medical indicators

Questionnaires such as the pain numeric rating scale (PNRS), the Oswestry disability index (ODI), Roland and Morris disability questionnaire (RMDQ), and 3-level EuroQol Five-Dimensional Questionnaire (EQ) were used to obtain data regarding pain and the quality of life of the participants.



**FIGURE 1. Procedure followed in the study.** One hundred and forty individuals applied to participate in this study, but 10 individuals dropped out in the screening stage; therefore, 130 individuals were assigned to two groups (Exp. n = 65, Con. n = 65). During the 1-week adaptation process, four participants were excluded from the experimental group. During treatment, 4 participants from the control group and 6 from the experimental group were excluded, and a total of 116 participants completed the treatments. fifty-seven blood samples were used for laboratory calibration to establish assay conditions for nine immunological measurements. Ultimately, data of 30 individuals in the experimental group and 29 in the control group were analyzed. RMI, Rehabilitative Medical Indicators; CLS, Changes in Leukocyte Subpopulations; CCP, Changes in Cytokine Production.



**FIGURE 2. Structural image of the spinal thermal massage device.** A roller massages the muscles along the spine by moving cranially, caudally, and vertically for paraspinal massage and applies segmental acupressure at the basic strength presented in the program algorithm.

## 2.5 Source of blood samples

Blood samples for the culture and immunofluorescence assay were collected in evacuated Vacutainer blood collection tubes containing 75 USP sodium heparin (ref. 367871) (Becton Dickinson and Co., Franklin Lakes, NJ, USA). Blood for serum samples was drawn into BD Vacutainer SST II Advance blood collection tubes (ref. 367955) (Becton Dickinson and Co.). The samples were collected at approximately 9:00 AM and processed immediately.

## 2.6 Quantitation of leukocyte subpopulations and flow cytometry

Total white cell blood counts and differential counts (lymphocytes and monocytes) were estimated from whole blood using an autoanalyzer (NX-3000; SYSMEX Co., Kobe, Japan). Immunofluorescence was performed for the quantitation of lymphocyte subpopulations using whole blood and monoclonal antibodies according to the manufacturer's instructions. The antibodies (BioLegend, San Diego, CA, USA) against leukocyte surface molecules used in this study were FITC-anti-CD3 (clone UCHT1), FITC-anti-CD4 (clone RPA-T4), PE-anti-CD8a (clone RPA-T8), FITC-anti-CD19 (clone HB19), and PerCP-anti-CD56 (clone HCD56). The erythrocytes were lysed using red blood cell lysis buffer (BioLegend) and flow cytometric analysis was performed using an EPICS V flow cytometer (Coulter Corp., Hialeah, FL, USA).

## 2.7 Blood culture

Iscove's modification of Dulbecco's medium (IMDM) (GIBCO Life Technologies, Grand Island, NY, USA) was supplemented with 1% antibiotic/antimycotic solution (penicillin 100 units/mL, 100  $\mu$ g/mL streptomycin, and

250 ng/mL amphotericin B; Sigma Chemical Company, St. Louis, MI, USA), 5 mM 2-mercaptoethanol, and 200 mM L-glutamine (Sigma Chemical Company). Heparinized blood was mixed with supplemented IMDM at a ratio of 1:10. The blood suspension was incubated with purified anti-CD3 (1  $\mu$ g/mL) and anti-CD28 (1  $\mu$ g/mL) antibodies (Miltenyi Biotec GmbH, Bergisch Gladbach, Germany) for T cell stimulation, and 100 ng/mL purified human interleukin (IL)-2 (Miltenyi Biotec GmbH) or 1  $\mu$ g/mL lipopolysaccharide (LPS) (Sigma Chemical Company) for NK cell or inflammatory cell stimulation. After stimulation for 1 or 3 days in 48-well culture plates (Nunc, Roskilde, Denmark) at 37 °C and with 5% CO<sub>2</sub>, the supernatants were recovered and frozen at -80 °C until analysis.

## 2.8 Enzyme-linked immunosorbent assay

The cytokine levels in the culture supernatants were measured using an enzyme-linked immunosorbent assay set (MAX Deluxe Set; BioLegend) according to the manufacturer's instructions.

## 2.9 Statistics

To control the difference between the groups at baseline, the data were processed using the analysis of covariance (ANCOVA) using the baseline value as a covariate. Two main effects (group and time effects) and an interaction effect (group  $\times$  time) were analyzed using ANCOVA, and post-hoc analysis was performed to evaluate the differences between the groups at each instance of measurement to check if any of the effects were significant. Data are presented as mean and standard error adjusted for the baseline. The criterion for statistical significance ( $\alpha$ ) was 0.05.

**TABLE 1. Changes in pain-related measures.**

	Group	At 4 weeks	ES	At 8 weeks	ES
PNRS	CON (n = 29)	4.19 (0.15)		3.95 (0.19)	
	EXP (n = 30)	3.95 (0.15)**	1.08	2.71 (0.18)**	1.22
ODI	CON (n = 29)	49.88 (1.36)		51.25 (2.07)	
	EXP (n = 30)	44.30 (1.33)*	0.69	37.94 (2.03)**	1.08
RMDQ	CON (n = 29)	9.14 (0.46)		9.41 (0.56)	
	EXP (n = 30)	7.66 (0.45)*	0.54	7.01 (0.54)**	0.73
EQ	CON (n = 29)	0.48 (0.01)		0.46 (0.02)	
	EXP (n = 30)	0.53 (0.01)**	0.73	0.56 (0.02)**	0.94

Values are expressed as mean (standard error) adjusted for the baseline value. Asterisks indicate significant group differences each time points (\* $p < 0.05$ , \*\* $p < 0.01$ ).  $ES \leq 0.20$ , effect Size (ES) is small;  $ES = 0.50$ , ES is medium; and  $ES \geq 0.80$ , ES is large.

### 3. Results

#### 3.1 Pain and quality of life

First, we examined the pain and quality of life perceived by the participants using four self-reported tests. For all measurements, the ANCOVA was performed using the baseline value as a covariate. In PNRS, the group effect was significant ( $p < 0.01$ ), but the time and interaction effects were not. The PNRS score in the experimental group was lower than that in the control group after both 4 weeks ( $p < 0.01$ ,  $ES = 1.08$ ) and 8 weeks ( $p < 0.01$ ,  $ES = 1.22$ ). The ANCOVA for ODI showed statistical significance in the group, time, and interaction effects ( $p < 0.01$ ). The ODI score was lower in the experimental group than in the control group after both 4 weeks ( $p < 0.05$ ,  $ES = 0.69$ ) and 8 weeks ( $p < 0.01$ ,  $ES = 1.08$ ). In RMDQ, the group effect was significant ( $p < 0.05$ ), but the time and interaction effects were not. The RMDQ score was lower in the experimental group than in the control group after 4 weeks ( $p < 0.05$ ,  $ES = 0.54$ ) and 8 weeks ( $p < 0.01$ ,  $ES = 0.73$ ). In EQ, the group ( $p < 0.01$ ) and interaction effects ( $p < 0.05$ ) were significant, but the time effect was not. The EQ score was higher in the experimental than in the control group after both 4 weeks ( $p < 0.01$ ,  $ES = 0.73$ ) and 8 weeks ( $p < 0.01$ ,  $ES = 0.94$ ) (Table 1, Fig. 3).

#### 3.2 Changes in leukocyte subpopulations

The changes in the count of peripheral blood leukocytes and the distribution of their subpopulations were evaluated for  $CD3^+$ ,  $CD4^+$ , and  $CD8^+$  T cells,  $CD19^+$  B cells, and  $CD56^+$ NK cells, which are reportedly low in elderly individuals [21–26]. The ANCOVA for leukocyte, lymphocyte,  $CD3^+$  T cell,  $CD4^+$  T cell,  $CD8^+$  T, and  $CD19^+$  B cell showed that there was no significant group, time, and interaction effects. For monocytes and  $CD56^+$  NK cells, the group effect was significant ( $p < 0.05$ ), but the time and interaction effects were not. Monocyte and  $CD56^+$  NK cell proportions were higher in the experimental group than in the control group after 8 weeks ( $p < 0.05$ ,  $ES = 0.68$ ,  $0.53$ , respectively) (Table 2, Fig. 4).

**TABLE 2. Changes in leukocyte subpopulations.**

	Group	At 4 weeks	At 8 weeks	ES
Leukocyte ( $\times 10^3/\mu\text{L}$ )	CON (n = 29)	6.44 (0.29)	6.63 (0.24)	
	EXP (n = 30)	6.68 (0.29)	6.35 (0.23)	
Lymphocyte (%) <sup>¶</sup>	CON (n = 29)	29.84 (1.67)	29.29 (54)	
	EXP (n = 30)	30.47 (1.64)	29.13 (1.52)	
Monocyte (%) <sup>¶</sup>	CON (n = 29)	6.80 (0.35)	6.74 (0.30)	
	EXP (n = 30)	7.26 (0.35)	7.85 (0.29)*	0.68
$CD3^+$ T (%) <sup>§</sup>	CON (n = 29)	57.78 (1.97)	56.43 (1.38)	
	EXP (n = 30)	55.88 (1.93)	59.13 (1.35)	
$CD4^+$ T (%) <sup>§</sup>	CON (n = 29)	35.50 (1.49)	37.99 (1.26)	
	EXP (n = 30)	35.75 (1.46)	34.88 (1.24)	
$CD8^+$ T (%) <sup>§</sup>	CON (n = 29)	14.00 (0.57)	11.68 (0.72)	
	EXP (n = 30)	14.20 (0.56)	11.98 (0.71)	
$CD19^+$ B (%) <sup>§</sup>	CON (n = 29)	4.66 (0.39)	5.68 (0.42)	
	EXP (n = 30)	4.14 (0.35)	5.11 (0.41)	
$CD56^+$ NK (%) <sup>§</sup>	CON (n = 29)	15.88 (1.12)	17.33 (0.96)	
	EXP (n = 30)	18.30 (1.10)	20.08 (0.94)*	0.53

Values are expressed as mean (standard error) adjusted for the baseline value.

Asterisks indicate significant group differences each time points (\* $p < 0.05$ ).

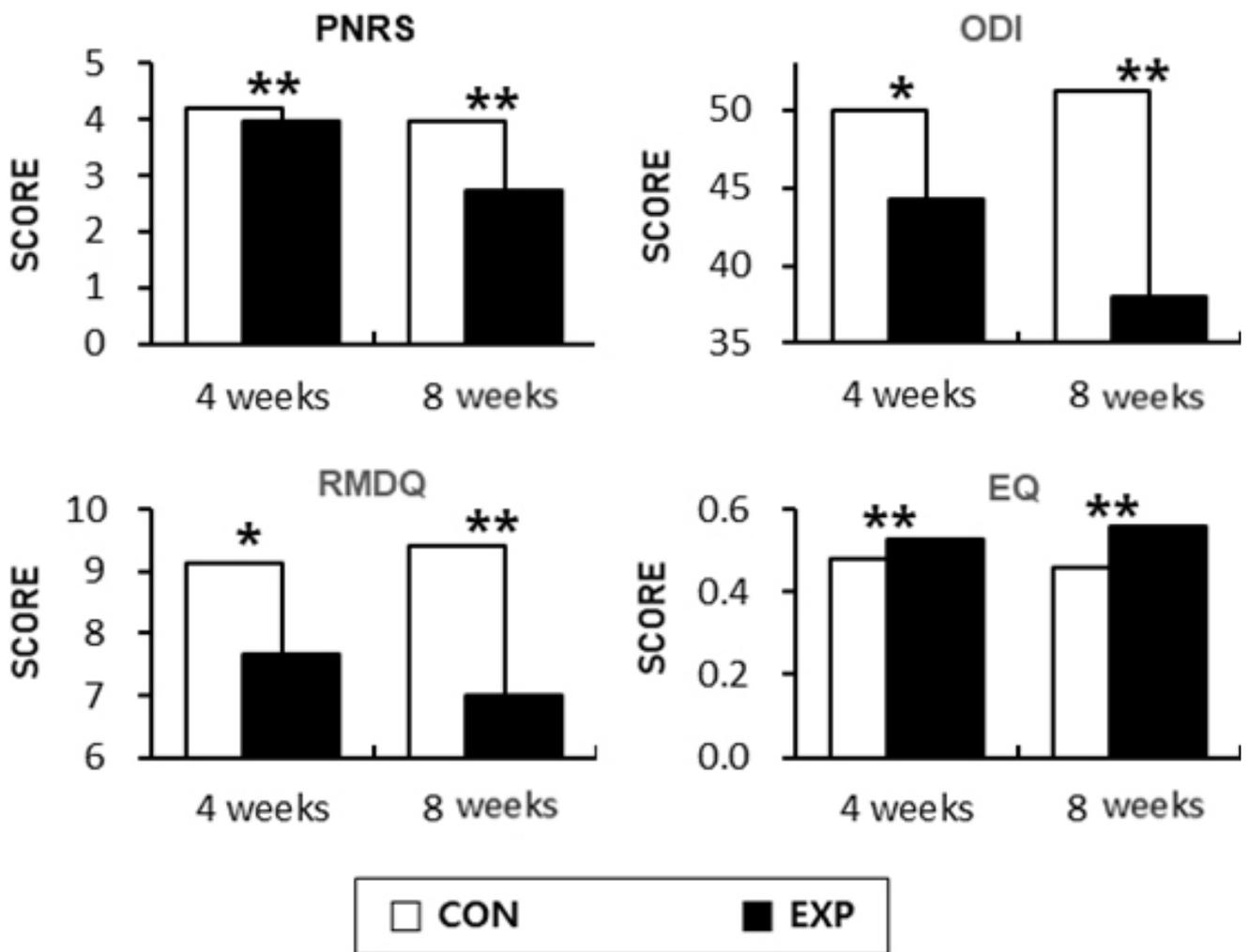
$ES \leq 0.20$ , effect Size (ES) is small;  $ES = 0.50$ , ES is medium; and  $ES \geq 0.80$ , ES is large.

<sup>¶</sup>, % of peripheral blood leukocytes.

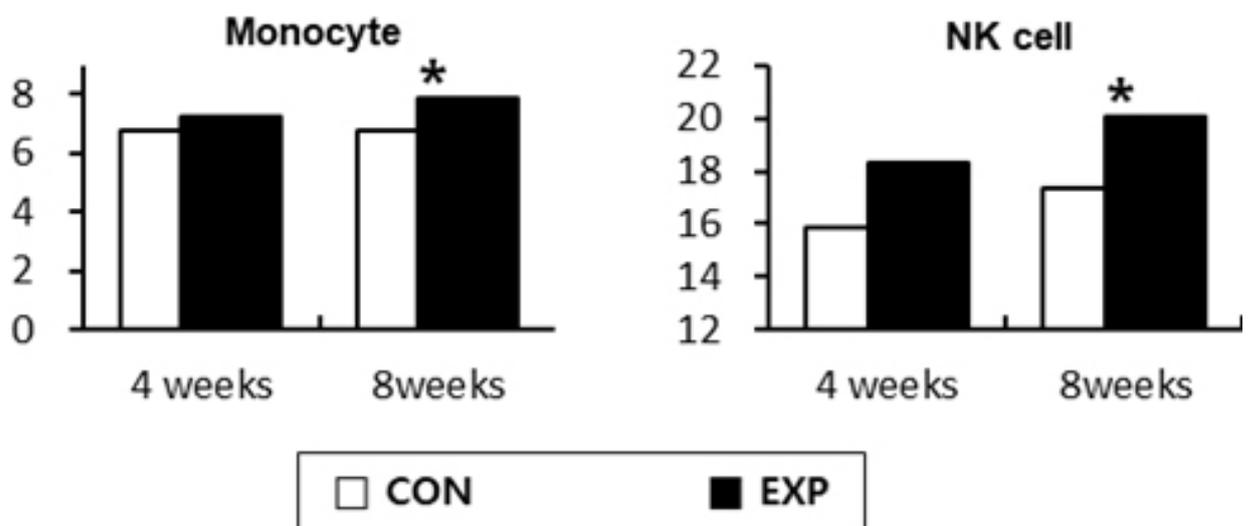
<sup>§</sup>, % of lymphocytes.

#### 3.3 Changes in cytokine production

The changes in cytokine production by T cells were evaluated; specifically, the IL-2, IL-4, and IFN- $\gamma$  levels were evaluated based on the findings of a previous study, which reported that their levels are low in elderly individuals [27]. For IL-2 production, the interaction effect was statistically significant ( $p < 0.05$ ), but the group and time effects were not. The IL-2 level



**FIGURE 3. Changes in pain-related measures.** Values are expressed as mean (standard error) adjusted for the baseline value. Asterisks indicate significant group differences each time points (\* $p < 0.05$ , \*\* $p < 0.01$ ).



**FIGURE 4. Changes in leukocyte subpopulations.** Values are expressed as mean (standard error) adjusted for the baseline value. Asterisks indicate significant group differences each time points (\* $p < 0.05$ , \*\* $p < 0.01$ ).

was lower in the experimental group than in the control group after 4 weeks ( $p < 0.05$ ,  $ES = 0.56$ ). There was no significant effect on IL-4 and IFN- $\gamma$  production.

Based on previous reports indicating that NK cell activity declines in elderly individuals [25, 28], the changes in IFN- $\gamma$  production following NK cell stimulation by IL-2 were

**TABLE 3. Changes in cytokine production.**

(pg/mL)	Group	At 4 weeks	ES	At 8 weeks
IL-2	CON (n = 29)	77.39 (17.93)	0.56	37.44 (11.52)
	EXP (n = 30)	23.12 (17.62)*		25.96 (11.33)
IL-4	CON (n = 29)	20.21 (3.73)		15.50 (2.713)
	EXP (n = 30)	11.53 (3.67)		9.46 (2.67)
IFN- $\gamma$ (T)	CON (n = 29)	19930 (3003.42)		26067 (3148.88)
	EXP (n = 30)	17402 (2952.86)		20837 (3095.87)
IFN- $\gamma$ (NK)	CON (n = 29)	3884 (1352.25)	0.61	4064 (1060.93)
	EXP (n = 30)	8313 (1329.37)*		4401 (1042.98)
TNF $\alpha$	CON (n = 29)	334 (33.81)		162 (29.43)
	EXP (n = 30)	274 (33.24)		231 (28.93)
IL-1 $\beta$	CON (n = 29)	2228 (195.45)		1385 (137.12)
	EXP (n = 30)	2086 (192.17)		1843 (134.81)
IL-6	CON (n = 29)	30786 (1867.33)		34682 (1772.99)
	EXP (n = 30)	27367 (1835.94)		31045 (1743.18)

Values are expressed as mean (standard error) adjusted for the baseline value. Asterisks indicate significant group differences each time points (\* $p < 0.05$ ).  $ES \leq 0.20$ , effect Size (ES) is small;  $ES = 0.50$ , ES is medium; and  $ES \geq 0.80$ , ES is large.

measured. Although there was no significant effect on the production of IFN- $\gamma$ , the group effect was close to the significance level ( $p = 0.058$ ). The IFN- $\gamma$  level was higher in the experimental group than in the control group after 4 weeks ( $p < 0.05$ ,  $ES = 0.61$ ) (Table 3, Fig. 5).

An increase in the production of proinflammatory cytokines by stimulated mononuclear cells has been observed in elderly subjects, and it may be related to several features of age-associated pathological events [29]. In this study, the production of tumor necrosis factor (TNF) $\alpha$ , IL-1 $\beta$ , and IL-6 after LPS stimulation of whole blood cells was also analyzed. For TNF $\alpha$  secretion, the interaction effect was statistically significant, but the group and time effects were not. This resulted from a significant reduction in the level of TNF $\alpha$  in the control group at 8 weeks compared with that at 4 weeks. There was no significant effect on IL-1 $\beta$  and IL-6 production.

#### 4. Discussion

A paraspinal automated thermal massager was used in this study for myalgia, and its analgesic effect was confirmed. Our findings showed that thermomechanical massage using an automated device may induce an immunological response and reduce pain similar to manual massage performed by massage experts [30–32]. Rehabilitative medical indicators reflecting the quality of life also supported this finding. No adverse events were observed during this trial. These results suggest that individuals with chronic pain and patients with cancer with treatment-related symptoms [33] can use this device as a complementary treatment to manage their pain in the comfort of their homes.

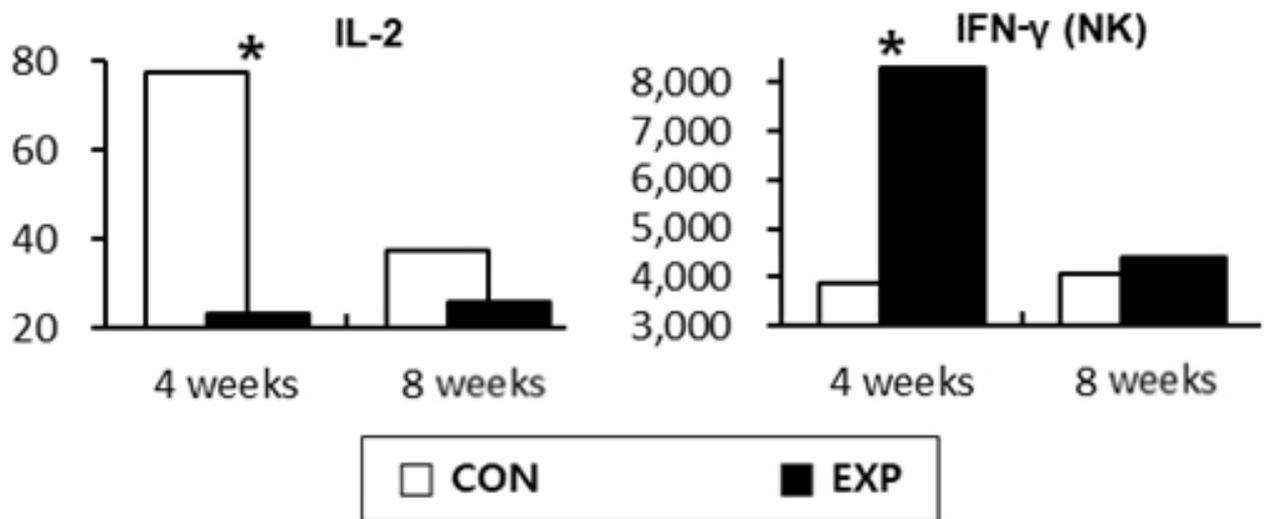
As hyperthermia has been widely used to treat cancer, data regarding the effects of hyperthermia on immune function have

been gathered. Hyperthermia leads to a relative decrease in CD4<sup>+</sup> T cell levels [20], an increase in the total lymphocyte count [34], enhancement of T cell proliferative response, and other beneficial effects [35].

In this study, no significant difference was observed in the total white blood cell count or proportions of lymphocytes and lymphocyte subpopulations, except for monocytes and CD56<sup>+</sup> NK cells (Table 2). These results were different from those of other studies that showed significant changes in lymphocyte and T cell counts after massage [36] or hyperthermia treatment [20] and an increase in T cell counts after STM (pilot study) [18]. Although it is not possible to directly compare these non-controlled data obtained from a few subjects ( $n = 4–11$ ), the discrepancy between our results and the results of hyperthermia treatment studies may be due to the different levels of heat provided by the equipment. Further research is needed to clarify this issue.

The monocyte and NK cell proportions were higher in the experimental group than in the control group after 8 weeks ( $p < 0.05$ ). Our finding for monocytes could not be compared with the results of other studies, because, to the best of our knowledge, an increase in monocyte proportions after massage or hyperthermia has not been documented. Nonetheless, this finding requires further investigation as monocyte function is also known to be impaired in elderly individuals [25] and as monocytes are key factors in the host defense system as phagocytic cells [37].

Although there are a few reports on the regulation of immune functions with massage therapy, data have shown that massage therapy increases NK cell counts in patients with AIDS [38, 39] and cancer [36]. Hyperthermia has been known to increase the count of NK cells [40]. These findings are in line with our results.



**FIGURE 5. Changes in cytokine production.** Values are expressed as mean (standard error) adjusted for the baseline value. Asterisks indicate significant group differences each time points ( $*p < 0.05$ ,  $**p < 0.01$ ).

Unexpectedly, the IL-2 level was lower in the experimental group than in the control group after 4 weeks ( $p < 0.05$ ). However, a decrease in the IL-2 level was not observed in the experimental group, most likely, owing to the substantial elevation in the IL-2 level in the control group, which could not be explained. The production of IL-4 and IFN- $\gamma$  from T cells stimulated with anti-CD3 was comparable between the groups. It is an interesting finding that massage may promote immunity via the attenuation of aberrant CD4<sup>+</sup> T subsets [41], although it was not addressed in the present study.

However, NK cell activity measured by interferon (IFN)- $\gamma$  production following IL-2 stimulation was significantly higher in the experimental group after 4 weeks ( $p < 0.05$ ). These results are similar to those of previous studies showing enhanced NK cell activity in patients with AIDS [38, 39] and cancer [36, 42], and they support the idea that NK cell activity can be activated by STM. Notably, this effect was not observed after 8 weeks of treatment in this study, suggesting that the NK-stimulating effect may not persist throughout STM treatment.

Several studies have reported that NK cells, among the leukocyte subpopulations, are particularly heat sensitive and thermal treatment enhances NK proliferation and activity [43, 44]. Furthermore, enhanced NK cell function is suggested as one of the mechanisms of action of hyperthermia to treat cancer [45]. If this view is accepted, then the effect of STM on NK cells demonstrated in this study can be interpreted as an effect of thermal treatment. NK cells have an important role in destroying cancer cells and virus-infected cells, and they are the main players in innate immunity against cancer and viral infections [46, 47]. In conclusion, this study suggests that STM may be beneficial for the prevention of these diseases by augmenting the first line of immune defense, such as monocytes and NK cells, in old-aged people.

The high levels of inflammatory cytokines in elderly individuals [28] are considered to be caused by underlying inflammatory diseases. Recent findings suggest that a reduction in the release of inflammatory cytokines via the inhibition of the TLR4 signaling pathway may be a mechanism by which

massage can relieve neuropathic pain [48]. Atanackovic *et al.* [40] demonstrated a marked but short-term increase in IL-6 and TNF $\alpha$  levels in patients with malignant diseases during the first 5–24 h after whole-body hyperthermia. However, STM did not alter the production of these cytokines (Table 3). Although further studies are necessary to provide better understanding, a possible explanation for the discrepancy is that short-term and long-term outcomes during STM treatment may differ.

A limitation of our study is that we were unable to randomly assign participants to the control group or experimental group, as discussed previously. The heterogeneity of participant characteristics of the two groups, although not statistically significant, may have distorted our results. Additionally, it should be noted that the peripheral blood leukocytes used in this study do not represent the full scope of individual immunity. Marked compositional differences have been reported between peripheral blood and primary/secondary lymphoid organs [49].

## 5. Conclusions

Our data showed that STM treatment can relieve pain and improve the perceived quality of life. STM treatment does not affect the distribution of T cells and B cells or cytokine production by T cells and inflammatory cells; however, it significantly increases the distribution and activity of peripheral blood NK cells. These results demonstrate that STM treatment, similar to manual massage, may also be beneficial for the prevention of NK-involved diseases, such as viral infections and tumor development, particularly in old-aged people susceptible to these diseases. However, further studies involving a larger cohort are required to draw a more definitive conclusion.

## AUTHOR CONTRIBUTIONS

KEK conceptualized and designed the study, prepared the materials, collected and analyzed the data, wrote the original draft, and reviewed and edited the manuscript. SYN conceptualized

and designed the study, prepared the materials, collected and analyzed the data, wrote and edited the manuscript, and was in charge of project administration. YSY, JSP, NRS, and SHP conceptualized and designed the study, prepared the materials, and collected and analyzed the data. SKP conceptualized and designed the study, prepared the materials, collected and analyzed the data, reviewed and edited the manuscript. IYC conceptualized and designed the study, prepared the materials, collected and analyzed the data, reviewed and edited the manuscript, and supervised the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Written informed consent was obtained from all the subjects before the study. This study adhered to the principles and recommendations of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board at the Presbyterian Medical Center (IRB no. 2017-06-022).

## ACKNOWLEDGMENT

Thank numerous individuals participated in this study.

## FUNDING

This research received no external funding.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY

All data generated for this study are included in the articles.

## REFERENCES

- [1] Harvey AM. Classification of Chronic Pain—Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. *The Clinical Journal of Pain*. 1994; 11: 163.
- [2] Augustin M, Maier K. Psychosomatic Aspects of Chronic Wounds. *Dermatology and Psychosomatics/Dermatologie Und Psychosomatik*. 2003; 4: 5–13.
- [3] Feine JS, Lund JP. An assessment of the efficacy of physical therapy and physical modalities for the control of chronic musculoskeletal pain. *Pain*. 1997; 71: 5–23.
- [4] Horner P, Abshari S, Grove C. *Massage*. Nursing. 2020; 50: 17–19.
- [5] Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Manual Therapy*. 2009; 14: 531–538.
- [6] Lee Y, Park BNR, Kim SH. The effects of heat and massage application on autonomic nervous system. *Yonsei Medical Journal*. 2011; 52: 982–989.
- [7] Kim D, Lee DW, Schreiber J, Im C, Kim H. Integrative Evaluation of Automated Massage Combined with Thermotherapy: Physical, Physiological, and Psychological Viewpoints. *BioMed Research International*. 2016; 2016: 2826905.
- [8] Buselli P, Bosoni R, BusèG, Fasoli P, La Scala E, Mazzolari R, *et al*. Effectiveness evaluation of an integrated automatic thermomechanic massage system (SMATH(R) system) in non-specific sub-acute and chronic low back pain - a randomized double-blinded controlled trial, comparing SMATH therapy versus sham therapy: Study protocol for a randomized controlled trial. *Trials*. 2011; 12: 216.
- [9] Muller J, Handlin L, Harlén M, Lindmark U, Ekström A. Mechanical massage and mental training programmes affect employees' anxiety, stress susceptibility and detachment-a randomised explorative pilot study. *BMC Complementary and Alternative Medicine*. 2015; 15: 302.
- [10] Kusnecov AW, Rabin BS. Stressor-induced alterations of immune function: mechanisms and issues. *International Archives of Allergy and Immunology*. 1994; 105: 107–121.
- [11] Starkweather AR, Witek-Janusek L, Nockels RP, Peterson J, Mathews HL. Immune function, pain, and psychological stress in patients undergoing spinal surgery. *Spine*. 2006; 31: E641–E647.
- [12] Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. *Physiological Reviews*. 2000; 80: 1055–1081.
- [13] Grace PM, Hurley D, Barratt DT, Tsykin A, Watkins LR, Rolan PE, *et al*. Harnessing pain heterogeneity and RNA transcriptome to identify blood-based pain biomarkers: a novel correlational study design and bioinformatics approach in a graded chronic constriction injury model. *Journal of Neurochemistry*. 2012; 122: 976–994.
- [14] Massart R, Dymov S, Millecamps M, Suderman M, Gregoire S, Koenigs K, *et al*. Overlapping signatures of chronic pain in the DNA methylation landscape of prefrontal cortex and peripheral T cells. *Scientific Reports*. 2016; 6: 19615.
- [15] Stein C, Clark JD, Oh U, Vasko MR, Wilcox GL, Overland AC, *et al*. Peripheral mechanisms of pain and analgesia. *Brain Research Reviews*. 2009; 60: 90–113.
- [16] Rittner HL, Brack A, Stein C. Pain and the immune system. *British Journal of Anaesthesia*. 2008; 101: 40–44.
- [17] Cameron MH. *Physical agents in rehabilitation: From research to practice*. W.B. Saunders: Philadelphia. 2003.
- [18] So CS, Sarath JV, Giolli RA, Gollapudi S. The effect of thermal massage on human T lymphocyte and natural killer cell function. *The Internet Journal of Alternative Medicine*. 2007; 6.
- [19] Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. *Transplant International*. 2009; 22: 1041–1050.
- [20] Ostapenko VV, Tanaka H, Miyano M, Nishide T, Ueda H, Nishide I, *et al*. Immune-related effects of local hyperthermia in patients with primary liver cancer. *Hepato-Gastroenterology*. 2005; 52: 1502–1506.
- [21] Linton PJ, Dorshkind K. Age-related changes in lymphocyte development and function. *Nature Immunology*. 2004; 5: 133–139.
- [22] Bjorkdahl O, Barber KA, Brett SJ, Daly MG, Plumpton C, Elshourbagy NA, *et al*. Characterization of CC-chemokine receptor 7 expression on murine T cells in lymphoid tissues. *Immunology*. 2003; 110: 170–179.
- [23] Fagnoni FF, Vescovini R, Passeri G, Bologna G, Pedrazzoni M, Lavagetto G, *et al*. Shortage of circulating naive CD8(+) T cells provides new insights on immunodeficiency in aging. *Blood*. 2000; 95: 2860–2868.
- [24] Vallejo AN. CD28 extinction in human T cells: altered functions and the program of T-cell senescence. *Immunological Reviews*. 2005; 205: 158–169.
- [25] Lutz CT, Moore MB, Bradley S, Shelton BJ, Lutgendorf SK. Reciprocal age related change in natural killer cell receptors for MHC class I. *Mechanisms of Ageing and Development*. 2005; 126: 722–731.
- [26] Della Bella S, Bierti L, Presicce P, Arienti R, Valenti M, Saresella M, *et al*. Peripheral blood dendritic cells and monocytes are differently regulated in the elderly. *Clinical Immunology*. 2007; 122: 220–228.
- [27] Grubeck-Loebenstein B, Wick G. The aging of the immune system. *Advances in Immunology*. 2002; 80: 243–284.
- [28] Solana R, Tarazona R, Gayoso I, Lesur O, Dupuis G, Fulop T. Innate immunosenescence: effect of aging on cells and receptors of the innate immune system in humans. *Seminars in Immunology*. 2012; 24: 331–341.
- [29] Fagiolo U, Cossarizza A, Scala E, Fanales-Belasio E, Ortolani C, Cozzi E, *et al*. Increased cytokine production in mononuclear cells of healthy elderly people. *European Journal of Immunology*. 1993; 23: 2375–2378.
- [30] Preyde M. Effectiveness of massage therapy for subacute low-back pain: a randomized controlled trial. *Canadian Medical Association Journal*. 2000; 162: 1815–1820.

- [31] Hernandez-reif M, Field T, Krasnegor J, Theakston H. Lower Back Pain is Reduced and Range of Motion Increased after Massage Therapy. *International Journal of Neuroscience*. 2001; 106: 131–145.
- [32] Goodfellow LM. The effects of therapeutic back massage on psychophysiological variables and immune function in spouses of patients with cancer. *Nursing Research*. 2003; 52: 318–328.
- [33] Taylor AG, Snyder AE, Anderson JG, Brown CJ, Densmore JJ, Bourguignon C. Gentle Massage Improves Disease- and Treatment-Related Symptoms in Patients with Acute Myelogenous Leukemia. *Journal of Clinical Trials*. 2014; 4: 1000161.
- [34] Tomiyama-miyaji C, Watanabe M, Ohishi T, Kanda Y, Kainuma E, Bakir HY, *et al*. Modulation of the endocrine and immune systems by well-controlled hyperthermia equipment. *Biomedical Research*. 2007; 28: 119–125.
- [35] Roberts NJ, Steigbigel RT. Hyperthermia and human leukocyte functions: effects on response of lymphocytes to mitogen and antigen and bactericidal capacity of monocytes and neutrophils. *Infection and Immunity*. 1977; 18: 673–679.
- [36] Hernandez-Reif M, Ironson G, Field T, Hurley J, Katz G, Diego M, *et al*. Breast cancer patients have improved immune and neuroendocrine functions following massage therapy. *Journal of Psychosomatic Research*. 2004; 57: 45–52.
- [37] Kantari C, Pederzoli-Ribeil M, Witko-Sarsat V. The Role of Neutrophils and Monocytes in Innate Immunity. *Contributions to Microbiology*. 2008; 15: 118–146.
- [38] Ironson G, Field T, Scafidi F, Hashimoto M, Kumar M, Kumar A, *et al*. Massage therapy is associated with enhancement of the immune system's cytotoxic capacity. *The International Journal of Neuroscience*. 1996; 84: 205–217.
- [39] Diego MA, Field T, Hernandez-Reif M, Shaw K, Friedman L, Ironson G. HIV adolescents show improved immune function following massage therapy. *The International Journal of Neuroscience*. 2001; 106: 35–45.
- [40] Atanackovic D, Nierhaus A, Neumeier M, Hossfeld DK, Hegewisch-Becker S. 41.8 degrees C whole body hyperthermia as an adjunct to chemotherapy induces prolonged T cell activation in patients with various malignant diseases. *Cancer Immunology, Immunotherapy*. 2002; 51: 603–613.
- [41] Sornkayazit K, Jumnainsong A, Phoksawat W, Eungpinichpong W, Leelayuwat C. Traditional Thai massage promoted immunity in the elderly via attenuation of senescent CD4<sup>+</sup> T cell subsets: A randomized crossover study. *International Journal of Environmental Research and Public Health*. 2021; 18: 3210.
- [42] Billhult A, Lindholm C, Gunnarsson R, Stener-Victorin E. The effect of massage on immune function and stress in women with breast cancer—a randomized controlled trial. *Autonomic Neuroscience*. 2009; 150: 111–115.
- [43] Azocar J, Yunis EJ, Essex M. Sensitivity of human natural killer cells to hyperthermia. *Lancet*. 1982; 1: 16–17.
- [44] Shen RN, Lu L, Young P, Shidnia H, Hornback NB, Broxmeyer HE. Influence of elevated temperature on natural killer cell activity, lymphokine-activated killer cell activity and lectin-dependent cytotoxicity of human umbilical cord blood and adult blood cells. *International Journal of Radiation Oncology, Biology, Physics*. 1994; 29: 821–826.
- [45] Hildebrandt B, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T, *et al*. The cellular and molecular basis of hyperthermia. *Critical Reviews in Oncology/Hematology*. 2002; 43: 33–56.
- [46] Whiteside TL, Herberman RB. The role of natural killer cells in immune surveillance of cancer. *Current Opinion in Immunology*. 1995; 7: 704–710.
- [47] Cerwenka A, Lanier LL. Natural killer cells, viruses and cancer. *Nature Reviews. Immunology*. 2001; 1: 41–49.
- [48] Wang Q, Lin J, Yang P, Liang Y, Lu D, Wang K, *et al*. Effect of Massage on the TLR4 Signalling Pathway in Rats with Neuropathic Pain. *Pain Research and Management*. 2020; 2020: 1–6.
- [49] Peters JH, Koenen HJPM, Fasse E, Tijssen HJ, IJzermans JNM, Groenen PJTA, *et al*. Human secondary lymphoid organs typically contain polyclonally-activated proliferating regulatory T cells. *Blood*. 2013; 122: 2213–2223.

**How to cite this article:** Ka-Eun Kim, Na-Ri Shin, Soon-Hi Park, Sang-Yun Nam, Yong-Soon Yoon, Soon-Kwon Park, *et al*. Modulation of the human immune status by spinal thermal massage: a non-randomized controlled study. *Signa Vitae*. 2021. doi:10.22514/sv.2021.144.