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ORIGINAL ARTICLE

Leg massage therapy promotes psychological relaxation and reinforces the first-line host defense in cancer patients

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Abstract
Purpose Patients with cancer suffer a wide range of physical symptoms coupled with psychological stress. Moreover, cancer chemotherapy induces immunosuppression and consequently causes respiratory infections. Massage therapy has been reported to reduce symptoms in cancer patients via an increase in psychosocial relaxation and to enhance and/or improve immune function.
Methods In the present study, we determined whether leg massage could induce psychosocial relaxation and activate the first line of the host defense system. To assess effects of rest and leg massage, 15 healthy volunteers rested on a bed for 20 min on the first day, and 3 days later the subjects received a standardized massage of the legs for 20 min with nonaromatic oil. Twenty-nine cancer patients also received the same standardized massage of the legs. Anxiety/stress was assessed before and just after the rest or the massage using the State-Trait Anxiety Inventory (STAI-s) and visual analogue scale (VAS). To evaluate oral immune function, salivary chromogranin A (CgA) and secretory immunoglobulin A (sIgA) levels were measured.
Results In healthy volunteers, rest significantly reduced VAS by 34% and increased sIgA by 61%. In contrast, leg massage significantly reduced both STAI-s and VAS by 24% and 63%, and increased both sIgA and CgA by 104% and 90%, respectively. In cancer patients, leg massage significantly decreased both STAI-s and VAS by 16% and 38%, and increased both salivary CgA and sIgA by 33% and 35%, respectively.
Conclusion Leg massage may promote psychosocial relaxation and reinforce a first-line host defense with an increase in secretion of antimicrobial peptides.

Keywords Cancer · Massage · Psychosocial stress · Immune function

Introduction

Patients with cancer suffer a wide range of physical symptoms coupled with psychosocial stress. Although tumor location and chemotherapy may cause severe physiological symptoms such as pain, nausea, and general fatigue, the burden of psychological stress, anxiety, and depression cannot be overemphasized. Massage therapies have been reported to produce beneficial physiological effects such as vasodilation, an increase in skin temperature, and body relaxation [1]. The underlying mechanisms are still unknown, but it is hypothesized that a reduction in lactic acid buildup in muscles, improving lymphatic and venous circulation, and the stimulation of healing of connective tissues may be involved [1]. In addition, massage has been proposed to promote psychosocial relaxation and reduce stress [2, 3].

Cancer chemotherapy induces immunosuppression and consequently causes respiratory infections. Massage

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therapy has been increasingly employed to reduce symptoms in cancer patients via psychosocial relaxation and a reduction in mental stress [4]. In addition, massage therapy has also been reported to enhance and/or improve immune function in cancer patients [2, 5] although this conclusion remains controversial [6].

The oral cavity is considered the first line of the host defense system against pathogens, which colonize and invade surfaces bathed by secretions. Saliva contains several specific defense factors such as secretory immunoglobulin A [7] and chromogranin A [8], which have been reported to have antibacterial and antifungal activities. Thus, activation of the oral immune defense system might reduce chemotherapy-induced respiratory infections. We recently found that back massage therapy promoted psychological relaxation and an increase in salivary chromogranin A release in healthy volunteers [9]. In addition, Groer and colleagues [10] also reported that back massage therapy increased salivary chromogranin A release with psychological relaxation. Therefore, massage therapy may promote psychological relaxation and reinforces the first-line host defense.

To evaluate level of anxiety or psychosocial stress, subjective assessment methods such as State-Trait Anxiety Inventory (STAI) score or the visual analogue scale (VAS) are widely used [11, 12]. STAI consists of two separate, self-report scales for measuring the distinct concepts of state and trait anxiety [11]. The state anxiety (STAI-s) scale can measure the temporary and situation anxiety state accompanied by excitement of autonomic nerves, and the trait anxiety (STAI-t) score is the individual characteristic in which state anxiety easily evokes a stress state [11]. Heart rate is also a good index for evaluation of mental stress. It has been reported that anxiety and mental stress are positively correlated to heart rate [13, 14].

In the present study, we determined whether leg massage could induce psychosocial relaxation and activate the first-line host defense system.

Methods

With the approval of our university ethics committee and informed consent, 15 healthy volunteers (age, 21.3 ± 1.1 years) and 29 cancer inpatients (age, 64.6 ± 12.8 years, male/female ratio = 18/11: lung cancer, $n = 26$; rectal cancer, $n = 2$; malignant lymphoma, $n = 1$) receiving chemotherapy with or without palliative therapy were enrolled, because power analysis using preliminary data suggested that more than 11 subjects would be needed. Most patients did not need opioid medication, although one patient required oral oxycodone 20 mg/day for cancer pain.

Assessment of anxiety

We used STAI-s score, VAS [0 (no stress) to 100 mm (the worst stress imaginable)], and heart rate to assess anxiety/mental stress.

Measurement of chromogranin A and secretory immunoglobulin A in saliva

Saliva for measurement of chromogranin A and secretory immunoglobulin A was collected with a cotton swab into special sampling tubes (Salivettes; Sarstedt, Nümbrecht, Germany) and by passive drool using a straw into a plastic tube, respectively. Tubes were then centrifuged for 3 min at 1,500*g* to obtain clear saliva, which was stored at −80°C until assay. Both salivary chromogranin A and secretory immunoglobulin A were assayed using an enzyme immunoassay kit according to the manufacturer's instructions (YKO70 Human Chromogranin A, EIA kit; Yanaihara Institute, Shizuoka, Japan, and Salivary Secretory IgA Indirect Enzyme Immunoassay Kit; Salimetrics, State College, PA, USA, respectively). Chromogranin A levels were corrected for salivary protein, which was determined using the Bio-Rad Protein assay kit, and expressed as pmol/mg protein. Intraassay maximal coefficient of variation was 8.15% for chromogranin A and 6.99% for secretory immunoglobulin A; interassay maximal coefficient of variation was 12.42% for chromogranin A and 8.93% for secretory immunoglobulin A.

Research protocol

Healthy volunteers

After the subjects had rinsed their mouth with water and an electrocardiogram (ECG) was recorded, they rested on a bed for 10 min. Each subject completed the state section of the STAI, and anxiety was assessed with STAI score and heart rates. The saliva was also sampled. Then, they rested on a bed for another 20 min as control, after which time assessment of anxiety and collection of saliva were repeated. Three days later, after the same subjects had rinsed their mouth with water and rested on a bed for 10 min under ECG monitoring, they received a standardized massage of the legs for 20 min with nonaromatic oil. Assessment of anxiety and collection of saliva were performed just before and after leg massage.

Cancer patients

After the subjects had rinsed their mouth with water and an ECG was recorded, they rested on a bed for 10 min. Then, the patients received a standardized massage of the legs for

20 min with nonaromatic oil. Assessment of anxiety and collection of saliva were performed just before and after leg massage.

Statistics

Data are mean ± SD. Statistical analysis was appropriately performed using one-way analysis of variance (ANOVA) followed by Student–Neuman–Keuls test or pared t test as appropriate, with $P < 0.05$ considered significant.

Results

Healthy volunteers

Leg massage significantly decreased VAS and STAI-s score (Table 1). Rest also significantly reduced VAS but not STAI-s score (Table 1). Heart rate (HR) was not affected by either leg massage or rest (Table 1), although there was a significant correlation with STAI-s score ($r = 0.266$, $P < 0.05$). There was a significant correlation between STAI-s and VAS ($r = 0.755$, $P < 0.01$). Both salivary chromogranin A and secretory immunoglobulin A increased significantly after rest or leg massage (see Table 1). The increase in chromogranin A was significantly higher after massage than after rest (Table 1). There was significant correlation between secretory immunoglobulin A and chromogranin A (Fig. 1a: $r = 0.640$, $P < 0.01$). In addition, there was a significant correlation between STAI-s score and secretory immunoglobulin A or chromogranin A (Fig. 1b: $r = 0.290$, $P < 0.05$; Fig. 1c: $r = 0.290$, $P < 0.05$).

Table 1 Effects of rest and leg massage on State-Trait Anxiety Inventory (STAI-s) score, visual analogue scale (VAS), heart rate, and salivary chromogranin A (CgA) and secretory immunoglobulin A (sIgA) levels in healthy volunteers

	Before	Just after
STAI-s		
Rest	36.1 ± 4.3	32.7 ± 7.1
Massage	38.3 ± 7.4	29.4 ± 5.5**
VAS (mm)		
Rest	28.9 ± 14.7	19.1 ± 16.8*
Massage	35.7 ± 5.5	13.1 ± 10.5**
Heart rate (beats/min)		
Rest	73.3 ± 10.3	70.1 ± 5.7
Massage	73.3 ± 10.7	68.1 ± 8.1
sIgA (μg/ml)		
Rest	85.1 ± 42.0	137.5 ± 64.3**
Massage	81.6 ± 37.9	166.4 ± 83.6**
CgA (pmol/mg protein)		
Rest	8.40 ± 7.59	9.21 ± 2.91
Massage	6.93 ± 4.05	13.19 ± 6.46**#

Before, before rest or leg massage; Just after, just after rest or leg massage

Salivary CgA and IgA were measured with an enzyme immunoassay kit

Mean ± SD, *$P < 0.05$, **$P < 0.01$ versus "Before massage"; #$P < 0.05$ versus rest using one-way ANOVA followed by Student–Neuman–Keuls test

Cancer patients

Heart rate, VAS, and STAI-s score decreased significantly after leg massage (Table 2). There was a significant correlation between STAI-s score and VAS ($r = 0.640$, $P < 0.01$) but not between heart rate and STAI-s score or VAS. Both salivary chromogranin A and secretory immunoglobulin A increased significantly (see Table 2). However, there was no significant correlation between STAI-s score and chromogranin A or secretory immunoglobulin A.

Discussion

In the present study, decreases in STAI-s score and VAS indicated that leg massage could reduce mental stress, especially cancer-related psychophysical stress in cancer patients. The study of Oshima and colleagues [15] is useful to put our data into context to compare with oral anxiolytics. They reported that diazepam and trandospirone (5-HT1A agonist) significantly reduced STAI-s by ~4.5 in patients undergoing otolaryngological surgery. In our study, leg massage reduced STAI-s by 7–9. In contrast to pharmacological anxiolysis, leg massage will not impair psychomotor function.

Massage therapy has been reported to not only reduce psychosocial stress but also enhance immune function in cancer patients [2, 5]. Moreover, massage therapy has also been shown to improve immune function in adult and adolescent human immunodeficiency virus (HIV) patients [16, 17]. Indeed, in the present study, leg massage significantly increased the release of salivary chromogranin A and secretory immunoglobulin A. Several reports [8, 18] suggest that chromogranin A has antibacterial and antifungal activities. Vasostantin-1, which is naturally processed from the N-terminal 1–76 of chromogranin A, inhibits the growth of bacteria and fungi [8, 18]. Salivary immunoglobulin A also acts as a first-line host defense against microbial invasion [7]. Groer and colleagues [10] reported that a 10-min nursing back rub increased salivary immunoglobulin A secretion. Therefore, massage therapy may reinforce host defense with an increase in secretion of

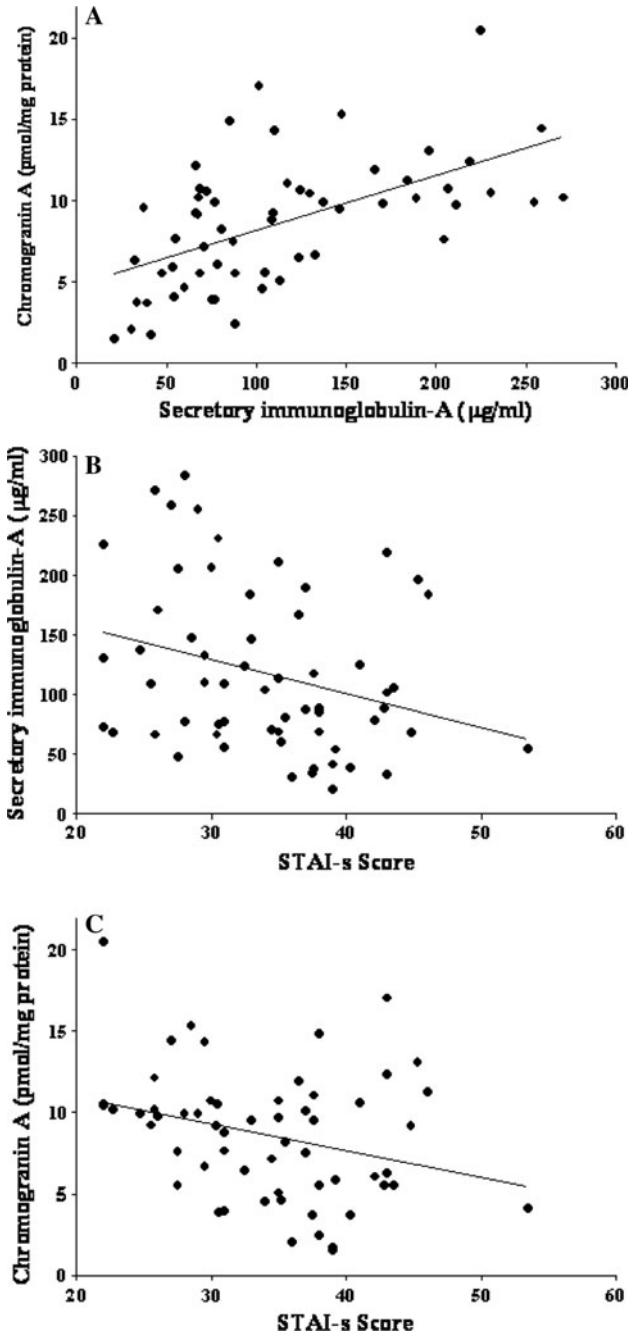

Fig. 1 Correlation between salivary chromogranin A and secretory immunoglobulin A (**a**: $r = 0.640$, $P < 0.01$) and between State-Trait Anxiety Inventory (STAI-s) score and secretory immunoglobulin A (**b**: $r = 0.290$, $P < 0.05$) or salivary chromogranin A (**c**: $r = 0.290$, $P < 0.05$) in healthy volunteers

antimicrobial peptides such as secretory immunoglobulin A and chromogranin A.

In healthy volunteers, there was a significant correlation between STAI-s score and salivary secretory immunoglobulin A or chromogranin A, which implies that mental relaxation may contribute to reinforcement of the oral immune system. However, in cancer patients, although leg massage significantly decreased and increased STAI-s score and salivary immunological biomarkers, respectively, there was no significant correlation between them. Cancer creates anxiety, anger, sadness, depression, and a greater sense of dread than other illnesses and disrupts all aspects of daily life including family, work, finances, and friendships [19]. As psychosocial stress in cancer patients could be more complicated than that in healthy volunteers, the complexity of mental status may result in the lack of correlation between STAI-s score and salivary immunological biomarkers.

Table 2 Effects of leg massage on STAI-s score, VAS, heart rate, and salivary chromogranin A (CgA) and secretory immunoglobulin A (sIgA) levels in cancer patients

	Before massage	Just after massage
STAI-s	43.8 ± 10.8	36.8 ± 9.2**
VAS (mm)	38.1 ± 22.2	23.8 ± 22.1**
Heart rate (beats/min)	79.2 ± 13.3	77.0 ± 11.8*
sIgA (μg/ml)	175.6 ± 104.4	233.8 ± 151.2*
CgA (pmol/mg protein)	6.16 ± 6.73	8.29 ± 8.51*

Salivary CgA and IgA were measured with an enzyme immunoassay kit

Mean ± SD, *$P < 0.05$, **$P < 0.01$ versus "Before massage" using paired t test

High occurrence of psychosocial distress severely impairs the quality of life in cancer patients. Despite this, ~30% of patients are unaware of the possibilities for psychosocial support, and 44% of patients refusing psychosocial support do not feel they require any help [20]. Although there is evidence for a general positive impact of massage in cancer for induction of psychosocial relaxation, the reality is that many patients will refuse such therapy. Our data showing both an improvement in anxiety/stress and immune function could be used to address this problem to improve patient engagement and compliance.

In conclusion, the present data suggest that leg massage therapy may promote psychosocial relaxation and reinforce the first-line host defense with an increase in secretion of antimicrobial peptides such as chromogranin A and secretory immunoglobulin A.

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