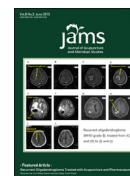


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## CLINICAL CASE REPORT



# Cancer-related Fatigue in Patients with Advanced Cancer Treated with Autonomic Nerve Pharmacopuncture

Ji-hye Park<sup>1</sup>, Hyung-jun Jeon<sup>1</sup>, Hwi-joong Kang<sup>1</sup>, In-Sook Jeong<sup>2</sup>,  
Chong-kwan Cho<sup>1</sup>, Hwa-seung Yoo<sup>1,\*</sup>

<sup>1</sup> East West Cancer Center, Dunsan Korean Medical Hospital of Daejeon University, Daejeon, South Korea

<sup>2</sup> Graduate School of Health and Sport, Daejeon University, Daejeon, South Korea

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### KEYWORDS

advanced cancer;  
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mountain ginseng  
pharmacopuncture

### Abstract

The purpose of this study was to observe the effects of autonomic nerve pharmacopuncture (ANP) treatment on cancer-related fatigue (CRF) in patients with advanced cancer. This observational case study was conducted at the East West Cancer Center of Daejeon University's Dunsan Korean Medical Hospital. Two patients were observed. One patient was diagnosed with left thymic cancer metastatic to the left pleura. The other patient had terminal-stage cervical cancer with iliac bone and lumbar 5 metastases. We injected mountain ginseng pharmacopuncture (MGP) into acupoints alongside the spine (Hua-Tuo-Jia-Ji-Xue, EX B2). We examined the patients for CRF using the Korean version of the Revised Piper Fatigue Scale (RPFS-K), which is a self-assessment tool. The scores on the RPFS-K for both patients tended to decrease during the treatment. Laboratory findings, including hematological changes, were also checked. Liver and renal function tests showed that the treatment was safe. Although further large-population studies are necessary, this case study suggests that ANP has a favorable effect on CRF in patients with advanced cancer.

\* Corresponding author. East West Cancer Center, Dunsan Korean Medical Hospital of Daejeon University, 176-75 Daedukdaero, Seo-gu, Daejeon 302-122, South Korea.  
E-mail: [altyhs@dju.kr](mailto:altyhs@dju.kr) (H.-S. Yoo).

## 1. Introduction

Fatigue in patients with advanced cancer is a commonly seen symptom. Cancer-related fatigue (CRF) has been defined by the United States National Comprehensive Cancer Network as “A distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment and is disproportionate to the level of recent activity, is not relieved by rest and interferes with usual daily activities” [1]. Fatigue and anorexia are the top two symptoms that bother patients with cancer, and these symptoms have a significant impact on the quality of life, leading to a poor prognosis, even in the course of after-treatment [2].

Liu et al [3] reported the result of a retrospective cohort study of the symptoms and the survival rate of 256 advanced cancer patients experiencing fatigue, and CRF was identified as a factor closely related to survival [3]. CRF often occurs during the course of radiation therapy or chemotherapy, or is caused by the cancer itself, as well as malnutrition, pain, decreased physical activity, emotional distress, insomnia, and hypothyroidism [4]. When the cause of the fatigue is apparent, medication is attempted. For example, if anemia, insomnia, and/or depression are identified as the causes of fatigue, anti-depressants, corticosteroids, and mental stimulant therapy can be used [5], however, such Western medicines may induce side effects [6]. Recently, Zeng et al [7] published a meta-analysis of randomized controlled trials of acupuncture for the treatment of CRF, and Su et al [8] published a systematic review of randomized clinical trials of Chinese herbal medicine for the treatment of CRF. Nevertheless, few clinical reports of the use of pharmacopuncture for treating cancer-related CRF have been published.

Autonomic nerve pharmacopuncture (ANP) is a therapy based on subcutaneous injection of mountain ginseng pharmacopuncture (MGP) into the acupoints alongside the spine (Hua-Tuo-Jia-Ji-Xue, EX B2) [9]. EX B2 is located at the branches of the autonomic nervous system [10]. The rationale for this approach is that subcutaneous MGP injection directly into the EX B2 acupoint is expected to enhance the balance in the autonomic nerve function, resulting in a positive effect on CRF. Here, we report a reduction in CRF for patients with advanced cancer after ANP.

## 2. Case Presentation

### 2.1. Materials

One milliliter from a 20-mL solution of MGP was injected into 10 EX B2 acupuncture points. Each 20-mL pharmacopuncture vial contained 3 g of mountain ginseng (15%). The process for preparing the MGP consisted of washing an entire mountain ginseng plant, extracting the active ingredient by distillation for 4 hours (pH 7.35–7.45) in a clean room, filtering it twice, and sealing in 20-mL aliquots in sterilized glass containers [9].

### 2.2. Methods

In Case 1, ANP was injected into the sites corresponding to the T1, T2, T3, T4, T5, T6, T7, T8, T9, and T10 0.5 cun lateral on the both sides of the intervertebral joint. In Case 2, ANP was injected into the sites corresponding to the L1, L2, L3, L4, L5, S1, S2, S3, S4, and S5 0.5 cun lateral to both sides of each intervertebral joint. The acupuncture points were chosen from the transport points associated with the organs affected by the cancer.

The Revised Piper Fatigue Scale (RPFS), a tool for assessing CRF in cancer patients, was developed in the United States [11]. Lee [12] modified this form and developed a Korean version of the RPFS (RPFS-K) with a total of 19 questions in the active area, emotional area, sensory area, and cognitive/mood area. All patients completed the RPFS-K questionnaire before treatment, each day after treatment, and at the end of treatment. Cronbach’s alpha was used to estimate the reliability of this assessment tool. It yields a value between 0 and 1, with scores closer to 1 indicating a higher reliability. For the RPFS-K, the reliability score was 0.93, which confirmed its reliability and validity [13].

### 2.3. Case 1

Case 1 involved a 40-year-old female patient. The patient was admitted from March 30, 2014 to April 12, 2014. In February 2009, the patient had been diagnosed with thymic cancer with metastasis to the left (Lt.) pleura. Common complaints were fatigue, fever, anorexia, and itching (face, anterior neck). Laboratory findings showed that after four ANP treatments, the white blood cells had increased to  $7190 \times 10^3/\text{mm}^3$  on April 7, 2014, compared to  $5410 \times 10^3/\text{mm}^3$  before treatment on March 31, 2014. The hemoglobin level had remained unchanged, whereas the erythrocyte sedimentation rate had decreased from 53 mm/h to 33 mm/h. The patient had been experiencing both itching and swelling of the thyroid gland site on admission. A laboratory test at admission showed a thyroglobulin antigen (Ag) level of 1000 ng/mL, indicating inflammation of the thyroid. After the ANP treatment, the thyroglobulin Ag level had decreased to 0.3 ng/mL (see Table 1).

On admission, we obtained the patient’s signature on the consent form and then injected ANP a total of four times at 2-day or 3-day intervals. On April 4, 2014, we did not inject ANP because of fever and itching, which were assumed to be due to an inflammatory response. The self-assessment total score was 166 at the time of admission and had decreased to 46 by the end of the treatment (see Figure 1).

### 2.4. Case 2

Case 2 involved a 61-year-old female patient. The patient was admitted from April 11, 2014 to May 12, 2014. The patient had been diagnosed with cervical cancer in November 2012. On February 11, 2014, positron emission tomography imaging showed tumor recurrence in the Lt. ilium and pelvic wall, as well as metastases to the iliac bone and L5 vertebra. Common complaints were fatigue, Lt.

**Table 1** Laboratory findings (Case 1).

Laboratory findings	Unit	Normal range	2014-03-31 (Before)	2014-04-07 (After)
WBC	10 <sup>3</sup> /mm <sup>3</sup>	4.5–11	5.41	7.19
Hemoglobin	g/dL	12–16	11.2 ▼	11.2 ▼
ESR	mm/h	0–20	53 ▲	33 ▲
Free T4	ng/dL	0.89–1.76	1.90 ▲	1.48
TSH	μIU/mL	0.35–5.5	0.4	0.21 ▼
Thyroglobulin Ab	U/mL	0–115	28.3	472.9 ▲
Thyroglobulin Ag	ng/mL	1.4–78	>1000.0 ▲	0.3 ▼

▲ indicates a higher than normal value and ▼ indicates a lower than normal value.

Ab = antibody; Ag = antigen; ESR = erythrocyte sedimentation rate; TSH = thyroid stimulating hormone; WBC = white blood cell.

lower limb edema and pain, lower back pain, and gait disturbance. Laboratory findings after the ANP treatment showed that the total protein level had slightly increased to 6.6 g/dL compared to 6.4 g/dL before the treatment. Albumin levels before and after ANP were similar. The level of  $\gamma$ -glutamyl transferase had decreased from 36 U/L to 21 U/L and that of C-reactive protein had decreased from 8.70 mg/dL to 5.79 mg/dL (see Table 2).

On admission, we obtained the patient's signature on the consent form and then conducted ANP (a total of 12 times) from April 14, 2014, to April 30, 2014. During the first 14 days of treatment, CRF decreased slightly. However, on April 29, 2014, the patient's lower limb pain began to worsen, which seemed to be caused by the progress of her spine metastatic lesion. The self-assessment total score was 157 at the time of admission and had decreased to 125 by the end of the treatment (see Figure 2).

### 3. Discussion

CRF is one of the most important factors affecting the quality of life of cancer patients and is found in almost 90%

**Table 2** Laboratory findings (Case 2).

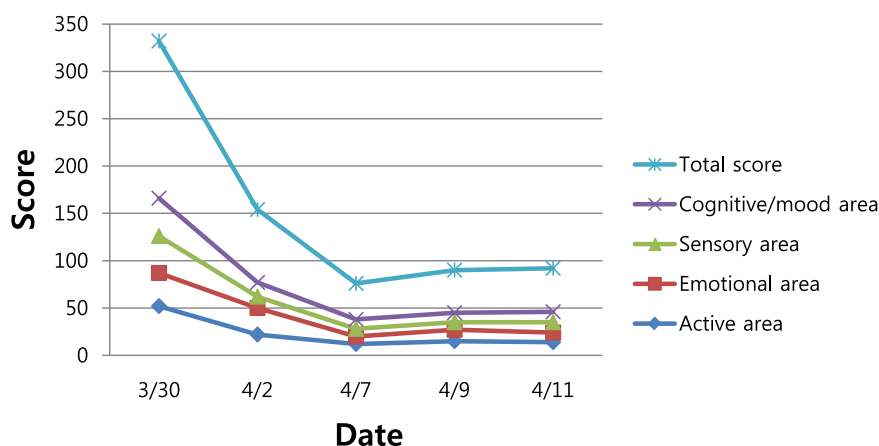
Laboratory findings	Unit	Normal range	2014-04-12 (Before)	2014-05-02 (After)
Total protein	g/dL	6.6–8.6	6.4 ▼	6.6
Albumin	g/dL	3.5–5.2	3.4 ▼	3.4 ▼
AST	U/L	0–31	27	20
ALT	U/L	0–34	27	14
ALP	U/L	30–120	111	96
r-GTP	U/L	7–32	36 ▲	21
CRP	mg/dL	0.5	8.70 ▲	5.79 ▲
WBC	10 <sup>3</sup> mm <sup>3</sup>	4.5–11	5.41	6.22
Hemoglobin	g/dL	12–16	11.7 ▼	9.4 ▼
ESR	mm/h	0–20	54 ▲	65 ▲

▲ indicates a higher than normal value and ▼ indicates a lower than normal value.

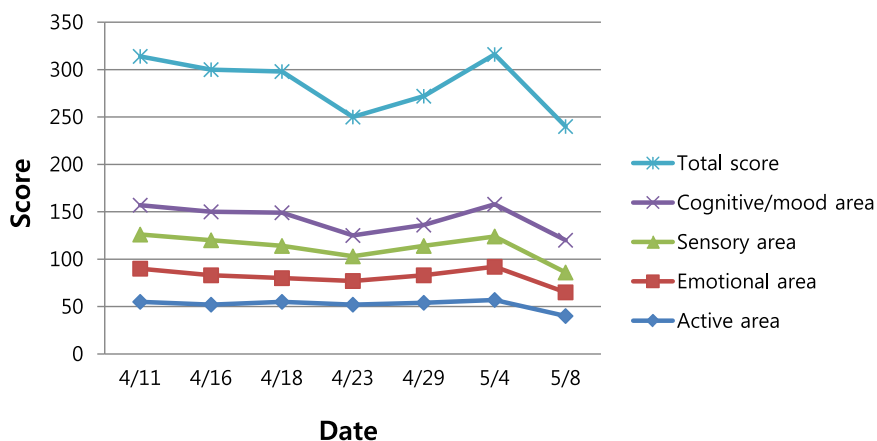
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRP = C-reactive protein; ESR = erythrocyte sedimentation rate, r-GTP =  $\gamma$ -glutamyl transferase, WBC = white blood cells.

of cancer patients [14]. Various mechanisms have been proposed to underlie CRF, including 5-hydroxytryptamine neurotransmitter dysregulation, vagal afferent activation, alterations in muscle and adenosine triphosphate metabolism, hypothalamic–pituitary–adrenal axis dysfunction, circadian rhythm disruption, and cytokine dysregulation [15]. Hyun et al [16] reported that acupuncture treatment reduced fatigue associated with lung cancer. Jeong et al [17] reported that bojungikki-tang helped to reduce CRF and improve the quality of life of patients with cancer. However, no clinical reports address the use of pharmacopuncture to treat cancer-related CRF.

ANP is a therapy that uses pharmacopuncture injection at EX B2. Direct injection of MGP into the acupuncture points anatomically analogous to the parts of the autonomic nerve branches is thought to improve the balance and activation of the autonomic function in the body. The autonomic nervous system is activated by the hypothalamus, spinal cord, and brain stem. This system regulates many activities of the human body. In the autonomic nervous system, nerve fibers



**Figure 1** Korean version of the Revised Piper Fatigue Scale (RPFS-K) scores during autonomic nerve pharmacopuncture treatment (Case 1). The scores of all factors were lower at the end of treatment compared to those on admission.



**Figure 2** Korean version of the Revised Piper Fatigue Scale (RPFs-K) scores during autonomic nerve pharmacopuncture treatment (Case 2). The total score decreased slightly. However, on April 29, 2014, the total score was slightly increased due to severe cancer-related pain. After the end of treatment, the measured total score was at its lowest.

originate from each ganglion on either side of the spine and innervate each internal organ. Norepinephrine or acetylcholine is secreted through the ganglion, and these hormones act on each organ, mediating the effects on the parasympathetic and sympathetic nerves [18].

In this research, 20 mL of distilled MGP was used for the ANP treatment. Mountain ginseng, which belongs to the family Araliaceae, is a wild perennial plant. It is also cultivated in the mountainous areas of Korea by using young ginseng plants or seeds [19]. The benefits of mountain ginseng that have been identified to date include adjustments of nerve functions, modulations of metabolic functions and fluids in the body, an antidiuretic effect, increased sexual desire and performance, increased resistance to stress, and enhanced digestion and antibody production [20]. Patients with advanced cancer have difficulty taking herbal medicines orally. Thus, ANP can be used in these patients to reduce CRF without the need for medicines taken orally.

In the cases of our two patients, the scores associated with CRF, measured using the RPFs-K, generally decreased. During the treatment period, patients did not complain of or present with any side effects of MGP. Our clinical data indicate that the use of Korean medicine for the treatment of CRF is effective. However, this study has a few limitations, including a scale that was too small, heterogeneity (two types of cancer), and a short treatment period. Large-scale studies and randomized-controlled studies on ANP for treating CRF in a cohort of patients with the same type of cancer need to be performed.

## Disclosure statement

The authors declare that they have no conflicts of interest and no financial interests related to the material of this manuscript.

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