Optical Examination of the Efficacy of Contact Needle Therapy for Chemotherapy-Induced Peripheral Neuropathy ~ Integration of Inspection in Kampo therapy with Color Spectrum Information~

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Abstract: Cancer chemotherapy-induced peripheral neuropathy (CIPN) deteriorates the patient's quality of life, often resulting in discontinuation of treatment with potentially effective chemotherapy. Contact needle therapy (CNT) is one of the traditional Japanese acupuncture methods based on the concept of Kampo (Japanese traditional) medicine. CNT on CIPN has been considered effective empirically, but an objective evaluation has proven difficult. We have focused on the oxygen saturation besides the symptom score. We have already proposed optical path-length matrix method (OPLM) for estimating oxygen saturation of the skin, which may help in locating peripheral tissue damage, including neuronal damage. Four patients with CIPN were treated with CNT. The severity of CIPN was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) ver.4 and FACT/GOG-Ntx before and after CNT. We also measured oxygen saturation and hemoglobin concentration at the right toe-tip. Correlations among the values were calculated as correlation coefficients. There were significantly improvements in FACT/GOG Ntx and hemoglobin post-CNT than in pre-CNT ($p < 0.05$). The oxygen saturation showed broad correlation ($0.5<|r|<1$) with hemoglobin. The oxygen saturation of skin reflects tissue injury and blood stagnation status, and can help in objective evaluation by measuring skin color spectrum. CNT might be considered as one of the safe and effective alternative therapeutic options for CIPN. Our method of evaluation using skin color spectrum information integrates, in a sense, the inspection in Kampo (Japanese traditional medicine) therapy and scientific methodology.

Keywords: Japanese traditional (Kampo) medicine, oxygen saturation, skin color spectrum, Chemotherapy induced peripheral neuropathy (CIPN), Contact Needle Therapy (CNT), Acupuncture

1 INTRODUCTION

Cancer chemotherapy-induced peripheral neuropathy (CIPN) is one of the most serious problems in clinical practice which can sometimes result in the discontinuation of subsequent treatment [1, 2]. CIPN is a well-known adverse effect of taxanes, platinum analogues, vinca alkaloids, and molecular target drugs such as bortezomib [3]. Taxane-induced neuropathy stems from damage to microtubules of the neuraxis, mainly presenting as a 'gloves-and-socks' type sensory disturbance [4]. Platinum analogues such as cisplatin and oxaliplatin damage nerve cells directly, followed by damage to the neuraxis [5]. Moreover, with oxaliplatin, acute accumulation-related disorder also occurs, and acute peripheral neuropathy is induced by a low-temperature stimulus that is known to be reinforced [6]. To prevent CIPN, calcium and magnesium infusions, glutathione, and anticonvulsants (carbamazepine) are used, but their efficacy is limited. Anticonvulsants, tricyclic antidepressants, alpha-lipoic acid, and opioids are often used for the treatment of CIPN [2, 7], with limited benefit. Abrogation of chemotherapy is required to prevent exacerbation of symptoms; specific and effective curative treatments are lacking. With the increase in patients with cancer and cancer survivors, treatment that considers the quality of life (QOL) of patients together with prognostic improvement is increasingly required.

Kampo (Japanese traditional) medicine (including herbal therapy, acupuncture, and acupressure) is the most frequently used alternative and complementary medicine in Japan. Contact needle therapy (CNT) is one of the Japanese traditional methods of acupuncture in Kampo medicine, which was developed by Bunkei Ono. Disposable needles are used, which are not inserted but only settled on the acupuncture point to provide a minimal but effective stimulus to unblock the meridian. The aim of CNT is to improve the patients' condition regardless of the underlying disease by regulating the flow of Qi. This method has many advantages; it is safe, painless, easy to perform, and has a low risk of infection.

From ancient times, it has been stated that the larger the needle and the deeper it is inserted, the stronger the

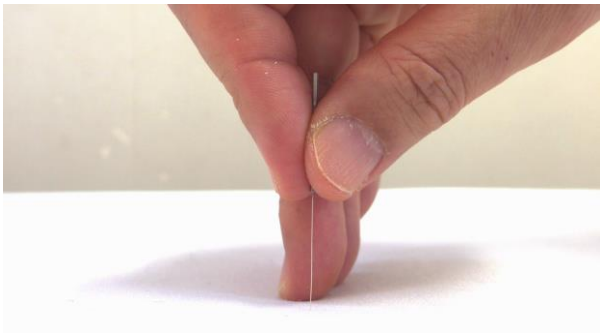
stimulation. If the stimulation is too strong, the patient's condition becomes worse, especially if their constitution is weak. CNT is known as a method of weak stimulation. In this aspect, CNT is effective and appropriate for treating cancer patients (Fig. 1).

Recently, a clinical pilot trial of acupuncture for the prevention or treatment of CIPN was conducted [8]. The effect of CNT has also been evaluated in case series [9], but symptom evaluation is subjective, and objective evaluation is necessary. CNT is thought to change the blood flow and tissue oxygen saturation according to the mechanism of acupuncture, and increasing blood flow might make tissue oxygen saturation increase. So we evaluated physiological relation among CNT, blood flow, and oxygen saturation.

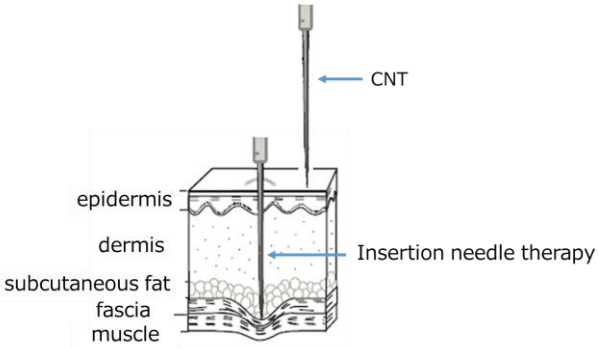
Skin is the largest organ of human body which can easily be observed non-invasively, but objective assessment of skin status is difficult. Previously, we proposed the optical path-length matrix (OPLM). OPLM is obtained as probabilistic density histograms of the optical path length in skin using Monte Carlo for multi-layered media (MCML); once the matrix is obtained, skin spectral reflectance can be calculated by accumulating all combinations of elements in the matrix and setting an absorption coefficient based on the Beer-Lambert law. We estimated oxygen saturation of skin using iterative OPLM [10]. OPLM is based on MCML, but can simulate skin spectral reflectance 27,000 times faster than MCML. As the inverse problem of MCML or OPLM is too complex to solve, iterating MCML or OPLM is necessary to estimate oxygen saturation. Hence, OPLM was proposed as a faster alternative of MCML. With the algorithm, oxygen saturation can be estimated from a skin color spectrum, which is measured with a handheld device. Oxygen saturation of skin may help in characterizing the pre-disease state.

In Kampo medicine, the "four examinations," including visual examination, listening/smelling examination, interview, and palpation, are defined as the methods for diagnosis [11]. Particularly, visual examination of the skin and tongue is one of the principal methods for diagnosis. Additionally, Kampo medicine contains many useful concepts for preventive medicine. For example, "Mibyou" (disease-oriented state: not a disease, but can easily become one if no cure is applied) is one of the most important concepts for preserving health and preventing illnesses from developing by the early recognition of signs of abnormalities and treating them. We previously developed a hyperspectral imaging system for tongue diagnosis [12, 13]. The system revealed correlation between Oketsu score (Table 1) and tongue color spectrum. Oketsu means blood stagnation in Kampo medicine. Oketsu score was previously determined by multivariate analysis conducted between symptoms described in the classics of Kampo medicine and clinical symptoms. Full points were added for severe level of symptoms, and half points for moderate level. However, the system is too huge and too expensive for clinical use. The other problem is that tongue color tends to change after several seconds [14], so color information has to be recorded quickly.

In this study, we focused on oxygen saturation and hemoglobin of skin as objective indices of skin properties, and studied the correlation among oxygen saturation, hemoglobin concentration, and neuropathy score.



(a)



(b)

Figure 1 Contact Needle Therapy (CNT)

(a) The method of holding the silver needle for CNT

(b) Diagram depicting the difference between inserted needling and CNT

2 MATERIALS AND METHODS

2.1 Subjects

Between July 2012 and January 2013, acupuncture treatment was offered to four patients who were diagnosed with CIPN. All patients agreed to receive acupuncture treatment in the form of CNT. We checked the patients' background (age, sex, and cancer types) and chemotherapeutic details. Four patients (three men, one women, mean age 63.5 years) received the best medical care and were additionally treated with CNT. Table 1 shows the patient characteristics. One patient had breast cancer and three had colorectal cancer. Each patient had undergone surgery and chemotherapy. Three of four received concurrent chemotherapy. Three had tumor-bearing status, and case 2 was receiving adjuvant chemotherapy. The chemotherapeutic agents associated with peripheral neuropathy were taxanes in case 2, and oxaliplatin in the other three cases (Table 2).

This study was approved by the Institutional Review Board and was conducted in accordance with the Code of Ethics of the World Medical Association (Helsinki Declaration).

2.2 Measuring oxygen saturation of skin with iterative optical path-length matrix (OPLM)

Diffuse spectral reflectance was measured with a spectrophotometer CM-700d (KONICA MINOLTA, INC., Tokyo, Japan), with a 3-mm diameter aperture and the specular component excluded (SCE) mode. Reflectance measurements were performed at two locations: the tip of the right first finger and dorsal surface of the right hand. Oxygen saturation and hemoglobin concentration at these two locations was estimated using the iterative OPLM as previously described [4,5] (Fig. 2).

2.3 Estimating melanin, hemoglobin and StO_2

Melanin, oxyhemoglobin, and deoxy-hemoglobin in skin are estimated from a multichannel visible spectrum image by using an inverse optical scattering technique. In this technique, first, a forward model of optical scattering is built to simulate the spectral reflectance of skin. Changing the variable parameters in the forward model, the simulation is repeated until the simulated spectral reflectance matches with the spectral reflectance at each pixel of the multi-spectral image. The principle of the proposed estimation technique was confirmed by imaging the human forearm under venous occlusion, venous and arterial occlusion, and by imaging a slapped region of the forearm [15]. Since we assumed the parameters of skin model such as thickness of epidermis layer empirically, the estimated hemoglobin concentration and oxygen saturation are relative values as was reported by Akaho [16].

Table 1. Oketsu score

Add full points for severe level of symptoms, and half points for moderate level. Oketsu is classified into three levels, with scores of < 20 as non-Oketsu, ≥20-<40 as moderate Oketsu, and ≥ 40 as severe Oketsu.

Symptoms	Male	Female
Dark-rimmed eyes	10	10
Areas of dark pigmentation on facial skin	2	2
Rough skin	2	5
Livid lips	2	2
Livid gingiva	10	5
Livid tongue	10	10
Telangiectasis / Vascular spider	5	5
Subcutaneous hemorrhage	2	10
Palmar erythema	2	5
Hemorrhoids	10	5
Dysmenorrhea	-	10
Resistance and/or tenderness on pressure of		
Right para-umbilical region	5	5
Left para-umbilical region	10	10
Umbilical region	5	5
Cecal region	5	2
Subcostal region	5	5

Table 2. Patient Characteristics

Case	1	2	3	4
Age/sex	70/F	54/F	57/F	73/F
Performance status	0	0	0	0
Primary lesion	colon	breast	colon	breast
Chemotherapeutic Agents	oxaliplatin	docetaxel paclitaxel	oxaliplatin	oxaliplatin
Chemotherapeutic Regimen	XELOX+ Bev	DOC PAC	mFOLFO +Bev	XELOX+ Bev
Past operations	Yes	Yes	Yes	Yes
Tumor-bearing	Yes	No	Yes	Yes

XELOX; oxaliplatin, capecitabine
Bev; bevacizumab
FOLFIRI; folinic acid, fluorouracil, irinotecan
FOLFOX; folinic acid, fluorouracil, oxaliplatin
DOC; fluorouracil, epirubicin, cyclophosphamide, docetaxel
PAC; paclitaxel, cyclophosphamide, doxorubicin

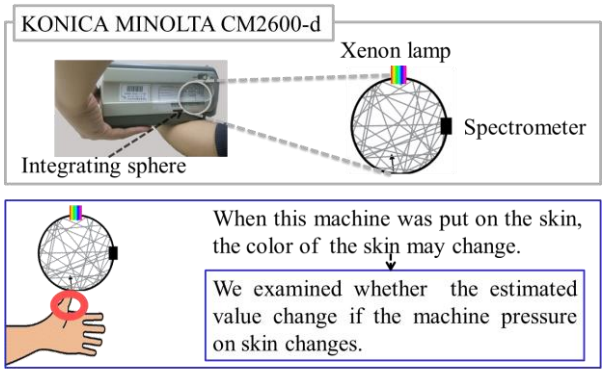


Figure 2 Measuring oxygen saturation of skin with iterative OPLM

2.4 Contact Needle Therapy (CNT)

The specific acupuncture protocols employed in this study are described below, point locations were as described in previously reported articles [9]. Disposable sterile silver needles (0.16×24 mm) were used and left in place for 30 seconds to 1 minute without insertion. Each patient received 4-6 treatments over 3 months, as described previously [9].

Acupuncture was performed in all cases by the same senior acupuncturist who had 20 years' experience. CNT was performed according to the medical diagnosis of meridian therapy. Acupuncture points used in this study were as following.

Points for all patients: CV12, CV4, ST25, KI2, well points of extremities.

Selected points: LR8, LR14, SP3, LR13, LU9, LU1, KI7, GB25, PC7, CV17, CV6, CV4, ST36, LU1, BL20, BL13, BL18, BL23.

Acupuncture points are determined based on "WHO Standard Acupuncture Point Locations in the Western Pacific Region." (http://www.wpro.who.int/publications/docs/WHOIST_26JUNE_FINAL.pdf)

2.5 Evaluation of neuropathy

The severity of CIPN was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and FACT/GOG-Ntx [17]. Clinical evaluation was performed before and after CNT because of the limitation of CTCAE for precise evaluation of symptoms. Objective evaluations were also obtained. Standardized questions regarding symptoms of neurotoxicity and examples of answers were used to facilitate a more accurate classification of patient-reported symptoms as a score of 0, 1, 2, 3, or 4. These grades were determined by physicians from patient interviews.

2.6 Statistical analysis

Correlation among the calculated values was computed by using the Pearson's product-moment correlation coefficient. The Wilcoxon signed rank test was performed to compare the values before and after CNT. A p-value of less than 0.05 was considered statistically significant. EZR v.1.36 software was used for statistical analysis [18].

3 RESULTS

Improvement of CIPN after CNT was found in one of the cases in CTCAE grading, while all patients showed improvement in the FACT/GOG-Ntx score. Hypoesthesia in a glove and/or stocking distribution was improved in all four patients. Both patients who complained of breakthrough pain showed apparent improvement (Table 3).

There was significant improvement in FACT/GOG Ntx scores post-CNT compared to pre-CNT scores ($p < 0.05$). The hemoglobin concentrations were significantly decreased post-CNT compared to pre-CNT levels ($p < 0.05$). The oxygen saturation showed broad correlation ($0.5<|r|<1$) with hemoglobin. The hemoglobin concentration and oxygen saturation showed little correlation with the FACT score.

Table 3. Effect of CNT

Case		1	2	3	4
CTCAE	before	2	1	1	1
	after	2	1	1	0
FACT/ GOG-NTX	before	11	6	4	9
	after	5	2	4	4
breakthrough pain	before	4	0	3	0
	after	0	0	1	0
Patients' evaluation		Improved	Improved	Improved	Improved
last responsible chemotherapy (month ago)		concurrent 12	26	concurrent 16	concurrent 1
Adverse effect of CNT		None	None	None	None

breakthrough pain: 0 (None) ～ 4 (Very severe)

4 DISCUSSION

In this investigation, significant improvement of CIPN was found post-CNT in FACT GOG/Ntx. CIPN of 3

patients with concurrent chemotherapy was not exacerbated, which may indicate the effectiveness of CNT as prophylaxis. In Patient 2 who stopped chemotherapy, CNT was effective in peripheral neuropathy even 2 years after the last chemotherapeutic dose. CIPN may spontaneously disappear over time in some cases and possibly in some patients in our study as well, but this would be unlikely while the responsible chemotherapy is ongoing, as well as after more than one year after the last dose. Patient 4 demonstrated remarkable improvement in pain, numbness, breakout pain, and discomfort of his legs.

Optical examination may provide a valuable, minimally invasive technique for clinical investigation of neural microcirculation. The hemoglobin concentrations were significantly decreased post-CNT compared to pre-CNT ($p < 0.05$). Although the FACT COG/Ntx showed no correlation with oxygen saturation nor with hemoglobin, the two latter factors showed a broad correlation. Yamamoto et al [19], showed a similar correlation of oxygen saturation at the dorsal surface of the hand with the Oketsu score, though not with oxygen saturation at the fingertip. The hemoglobin concentration had a small correlation with the oxygen saturation. These differences possibly arise from the status of microcirculation after chemotherapy. The blood flow to the patient fingertips after chemotherapy might be more likely to change compared to that in healthy individuals. Especially, blood stagnation might cause retention of blood in fingertips, which would lead to increased hemoglobin measurements.

These findings suggest that CNT improved peripheral blood flow especially for recurrent perfusion and might have reduced inflammation, which support the efficacy of CNT in CIPN. CNT might be considered as one of the safe and effective alternative therapeutic options for CIPN.

The oxygen saturation of skin reflects tissue injury and blood stagnation status, and can help in objective evaluation by measuring skin color spectrum. Although the change in oxygen saturation was not significant in this study, it showed broad correlation with hemoglobin. This study included only four patients, but it suggests that our method of evaluation using skin color spectrum information integrates, in a sense, the inspection in Kampo medicine and scientific methodology.

A prospective clinical trial should be carried out so that more patients can take advantage of the therapeutic properties of CNT. Future studies should examine the mechanism of action of CNT using objective evaluation by measuring skin color spectrum.

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