Journal of Traditional and Complementary Medicine 6 (2016) 135–139

Contents lists available at ScienceDirect

Journal of Traditional and Complementary Medicine

journal homepage: http://www.elsevier.com/locate/jtcme

Original article

Changes in urinary Cu, Zn, and Se levels in cancer patients after treatment with Sha Shen Mai Men Dong Tang

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ARTICLE INFO

Article history:
Received 2 November 2014
Received in revised form
24 November 2014
Accepted 11 December 2014
Available online 3 August 2015

Keywords:
chemoradiotherapy
head and neck cancer patients
ratio of Se to Cu
urine
ratio of Zn to Cu

ABSTRACT

Sha Shen Mai Men Dong Tang (SMD-2; 沙參麥冬湯 shā shēn mài dōng tāng) is a Chinese medicinal herb (CMH; 中草藥 zhōng cǎo yào) used to treat symptoms associated with cancer therapy. The objective of this study was to assess the effect of SMD-2 on the levels of urinary copper (Cu), zinc (Zn), and selenium (Se) in lung cancer patients and head and neck cancer patients receiving chemoradiotherapy. Forty-two head and neck cancer patients and 10 lung cancer patients participated in our clinical trial. Each patient received chemoradiotherapy for 4 weeks. In addition, each patient was treated with SMD-2 for 8 weeks, including 2 weeks prior to and after the chemoradiotherapy treatment. Comparison of urinary Cu, Zn, and Se levels and the ratios of Zn to Cu and Se to Cu at three time points in the two types of cancer were assessed using the generalized estimating equations (GEEs). After the patients received chemoradiotherapy for 4 weeks, SMD-2 treatment was found to be associated with a significant decrease in urinary Cu levels, whereas urinary Zn and Se levels increased significantly. In addition, the ratios of Zn to Cu and Se to Cu in the urine samples of these patients also increased significantly. Both the urinary Zn levels and the ratio of Zn to Cu in head and neck cancer patients were significantly higher than in lung cancer patients. Urinary Zn and Se levels and the ratios of Zn to Cu and Se to Cu, but not urinary Cu levels, increased significantly during and after treatment when assessed using the GEE model. The SMD-2 treatments significantly increased Zn and Se levels in the urine of head and neck cancer patients. Increased Zn and Se levels in urine strengthened immune system.

1. Introduction

In Taiwan, the practice of using Chinese medicine in combination with Western medicine to treat cancer patients is on the rise. In this study, we treated head and neck as well as lung cancer patients undergoing radiotherapy or chemotherapy with Sha Shen Mai Men Dong Tang (SMD-2; 沙參麥冬湯 shā shēn mài dōng tāng), a mixture of seven herbs. According to Chinese medicine, SMD-2 can "clear and nourish the lungs and stomach (清肺養胃 qīng fèi yǎng wèi)", "engender fluid (生津 shēng jīn)", repair damaged cells, and control the symptoms of dryness associated with cancer treatment. Western cancer treatment depends solely on the use of radiotherapy or chemotherapy, which unfortunately produces serious side effects. Short-term side effects of chemoradiotherapy include fatigue, nausea, vomiting, mucositis, myelosuppression, and neutropenia. These side effects generally occur within months of completion of chemotherapy.[1] A variety of Chinese medicinal herbs (CMHs; 中草藥 zhōng cǎo yào) have been used to minimize these side effects. A clinical study performed by Lan[2] in China indicated a significant reduction in oral mucosal symptoms in nasopharyngeal cancer patients who first received chemoradiotherapy and then SMD-2 treatments. Another study in China by Sung and Dong[3] showed that head and neck cancer patients who received

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Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

http://dx.doi.org/10.1016/j.jtcme.2014.12.004

chemoradiotherapy experienced oral dryness and had difficulty chewing and swallowing. The patients were then treated with SMD-2, and their symptoms improved tremendously.

Previous studies have shown that fluctuations in the levels of Se, Zn, and Cu in humans are indicators of cancer.[4,5] For example, high serum Cu levels and low serum Zn levels are markers of lung cancer.[6] Songchitsomboon et al[7] suggested that the use of serum Cu to Zn ratios as markers for the diagnosis of cancer or for staging tumors must be interpreted with caution. A double-blind, randomized study conducted by Lin et al[8] indicated that after head and neck cancer patients received chemoradiotherapy, Zn supplements repair cellular DNA, strengthen the immune system, and alleviate the severity of mucositis and dermatitis. As mentioned earlier, the levels of Zn, Se, and Cu fluctuate in cancer patients; therefore, monitoring the levels of these trace elements during cancer treatment may help in understanding the efficacy of cancer treatment, as well as provide an important tool in the diagnosis of cancer. The objective of this study was to assess the effect of SMD-2 on changes in urinary Cu, Zn, and Se levels in lung cancer patients and head and neck cancer patients receiving chemoradiotherapy.

2. Materials and methods

2.1. Study design and participant selection

Measurements of urinary Cu, Zn, and Se levels were obtained prior to and after SMD-2 treatment. This protocol was approved by the Institutional Review Board in China Medical University, and informed consent was obtained from patients prior to their participation. Ten lung cancer patients and 42 head and neck cancer patients participated in our study, which was conducted at a medical center in central Taiwan. Each patient was advised by medical personnel to take vitamins containing Zn and Se. Because of ethical considerations, a placebo group was not included in the study design. Each cancer patient was treated with radiotherapy (average dose, 5440 cGy) and chemotherapy (cisplatin, 60 mg/m^2 on Day 1; 5-fluorouracil, 500 mg/m^2/day on Days 1–5; and mitomycin C, 6 mg/m^2/day on Day 1 and Day 8) for 4 weeks. In addition, each patient received SMD-2 treatments for 8 weeks (2 weeks prior to receiving chemoradiotherapy, 4 weeks during chemoradiotherapy, and 2 weeks after the treatment). SMD-2 is a powder made of Adenophorae radix (南沙參 nán shā shēn), *Ophiopogon* tuber (麥門冬 mài mén dōng), *Polygonatum officinale* rhizome (玉竹 yù zhú), folium mori (桑葉 sāng yè), *Trichosanthes* root (天花粉 tiān huā fěn), semen dolichoris (白扁豆bái biǎn dòu), *Polygonatum odoratum* (葳蕤 wēi ruí), and *Glycyrrhiza* radix (甘草 gān cǎo). SMD-2 is prepared by a manufacturer in Taiwan with good manufacturing practices. We characterized SMD-2 with inductively coupled plasma/mass spectrometry (ICP/MS) and found it to contain Cu (27.6 ppm), Zn (85.7 ppm), and Se (0.38 ppm).

2.2. Measurement

Fresh spot urine samples were obtained from each cancer patient at three points during the trial (prior to, during, and after chemoradiotherapy). Specimens were stored at −70°C until metal analysis was carried out. An ICP/MS instrument (PerkinElmer ELAN DRC-e, Waltham, Massachusetts, US) was used to measure the Cu, Zn, and Se levels. Jones[9] and Heitland and Köster[10] have described this procedure in detail. The methodology for metal analysis and quality control has been published previously. The instrument detection limit for Cu, Zn, and Se using ICP/MS was 0.16 μg/L, 0.48 μg/L, and 0.29 μg/L, respectively. The method detection limits for Cu, Zn, and Se were 0.17 μg/L, 2.53 μg/L, and 0.30 μg/L, respectively. The precision (relative standard deviation) of measuring urinary metals was less than 5%. The recovery for measuring urinary metals was 106% for Cu, 102% for Zn, and 104% for Se.

2.3. Data collection and analysis

After measuring urinary metal levels, we calculated the ratios of Zn to Cu (Zn/Cu ratio) and Se to Cu (Se/Cu ratio). Data were collected using Microsoft Excel 2000 (Microsoft, Redmond, WA, USA) and analyzed by SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). Because the sample size in this study was limited, the nonparametric method was used. The differences in urinary metal levels (μg/L) for each intervention period were examined using the Mann–Whitney U test ($p < 0.05$). The urinary Cu, Zn, and Se levels and the ratios of Zn/Cu and Se/Cu in the two types of cancer at three-stage points were compared using the generalized estimating equations (GEEs).

3. Results

Table 1 presents the urinary Cu, Zn, and Se levels prior to, during, and after the treatment in patients with cancer of the head and neck who were treated using SMD-2. The level of Cu in the urine of these patients decreased to 25 μg/L after the treatment; however, the urinary Zn and Se levels increased to 578 μg/L and 78 μg/L, respectively, after the treatment. Furthermore, the Zn/Cu and Se/Cu ratios in the urine of these patients increased 111 times and 18 times, respectively.

Table 2 presents the urinary Cu, Zn, and Se levels prior to, during, and after the treatment in patients with lung cancer who were treated using SMD-2. Prior to treatment, the urinary Cu level in these patients was 25.9 μg/L on average, but after the treatment, the average urinary Cu level decreased to 8.55 μg/L, which was statistically significant. Furthermore, the urinary Zn levels increased by more than threefold after the treatment, and urinary Se levels doubled after the treatment, both of which were also statistically significant. In addition, the Zn/Cu and Se/Cu ratios in the urine of these patients increased significantly.

Table 3 presents a comparison of the urinary Cu, Zn, and Se levels and the ratios of Zn/Cu and Se/Cu in the two types of cancer at three time points using the GEE model. There was no significant difference in urinary Cu levels in patients suffering from the two types of cancer. Both urinary Zn levels and the ratio of Zn/Cu in patients with head and neck cancer were significantly higher than in those with lung cancer. However, there was no significant difference in the urinary Cu and Se levels (μg/L), or in the ratio of Se/Cu between the groups of cancer patients. In addition, urinary Zn and Se levels (μg/L) and the ratios of Zn/Cu and Se/Cu, but not urinary Cu levels, increased significantly during and after the treatment.

Table 1
Urinary Cu, Zn, and Se levels (μg/L) and ratios of Zn/Cu and Se/Cu prior to, during, and after the SMD-2 treatment in patients with cancer of the head and neck ($N = 42$).

	Prior to treatment	During treatment	After treatment	p_1*	p_2**
Cu	33.95 ± 52.00	18.82 ± 20.47	8.33 ± 6.81	<0.001	<0.001
Zn	212.2 ± 274.1	491.79 ± 718.8	790.8 ± 863.0	<0.001	<0.001
Se	37.44 ± 35.74	67.33 ± 59.45	115.83 ± 862.99	<0.001	<0.001
Zn/Cu	11.01 ± 15.30	32.72 ± 39.27	122.14 ± 114.37	<0.001	<0.001
Se/Cu	2.08 ± 2.20	4.84 ± 301	20.80 ± 16.46	<0.001	<0.001

*p_1 was calculated using paired t test between the periods prior to and during treatment.
**p_2 was calculated using paired t test between the periods prior to and after treatment.
SMD-2 = Sha Shen Mai Men Dong Tang.