



Treatment of Midnight-Noon Ebb-Flow Acupuncture for Chemotherapy-Induced Peripheral Neuropathy in Patients with Multiple Myeloma

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Abstract

Background: Chemotherapy-Induced Peripheral Neuropathy (CIPN) seriously affects the quality of life of patients with Multiple Myeloma (MM). Midnight-noon ebb-flow acupuncture has a potential role in the treatment of CIPN, but at present there have been no randomized clinical research studies to analyze the effectiveness of acupuncture for the treatment of CIPN, particularly in MM patients.

Methods: The MM patients (44 individuals) who met the inclusion criteria were randomly assigned into a solely methylcobalamin therapy group (1000 µg methylcobalamin was injected intravenously once daily) and an acupuncture combined with methylcobalamin (Met + Acu) group (methylcobalamin used the same way as above accompanied by four cycles of acupuncture). Of the patients, 39 out of 44 completed the treatment and follow-ups. The evaluating parameters included the Visual Analogue Scale (VAS) pain score, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire scores, and Electromyographic (EMG) nerve conduction velocity (NCV) determinations. We evaluated the changes of the parameters in each group before and after the therapies and made a comparison between the two groups.

Results: After 112 days (four cycles) of therapy, the pain was significantly alleviated in both groups, with a significantly higher decrease in the acupuncture treated group ($P < 0.01$). The patients' daily activity evaluated by Fact/GOG-Ntx questionnaires significantly improved in the methylcobalamin + midnight-noon ebb-flow acupuncture group ($P < 0.001$). The VAS in the methylcobalamin + midnight-noon ebb-flow acupuncture group improved significantly ($P < 0.001$).

Conclusion: The present study suggests that midnight-noon ebb-flow acupuncture combined with methylcobalamin in the treatment of CIPN showed a better outcome than methylcobalamin administration alone.

Keywords: Multiple myeloma; Chemotherapy-induced peripheral neuropathy; Midnight-noon ebb-flow acupuncture

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Abbreviations

MM: Multiple Myeloma; CiPN: Chemotherapy-Induced Peripheral Neuropathy; BiPN: Bortezomib-Induced Peripheral Neuropathy; TiPN: Thalidomide-Induced Peripheral Neuropathy; PN: Peripheral Neuropathy; TCM: Traditional Chinese Medicine; HIV: Human Immunodeficiency Virus; VAS: Visual Analog Scale Pain Score; FACT/GOG-NTx: Functional Assessment of Cancer Therapy Neurotoxicity Neurotoxicity rating Scale; NCV: Nerve Conduction Velocity; MCV: Motor Conduction Velocity; SCV: Sensory Conduction Velocity; ST36: Zusanli; ST40: Fenglong; SP6: Sanyinjiao; SP5: Shangqiu; HT7: Shenmen; HT5: Tongli; SI4: Wangu; BL58: Feiyang; KI3: Taixi; KI6: Zhaohai; PC6: Neiguan; SJ5: Waiguan; GB41: Zulinqi; GB34: Yanglingquan; LR3: Taichong; LR2: Xingjian; LU5: Chize; LU10: Yuji

Introduction

Multiple Myeloma (MM), a malignant disease, is characterized by a large number of abnormal proliferations of monoclonal plasma cells in the bone marrow. Clonal plasma cells and their secreted M proteins directly infiltrate tissues and organs, resulting in various clinical symptoms.

These are characterized by anemia, bone pain or osteolytic bone destruction, hypercalcemia, and renal insufficiency. In recent years, with the advent of new drugs and improvement of detection techniques, the diagnosis and treatment of MM have been incessantly improved and modified. Moreover, the survival time of patients with MM has been significantly prolonged, particularly the emergence of protease inhibitor bortezomib and immunomodulatory drugs thalidomide and lenalidomide. These have modified the treatment of MM completely and improved the response rate and survival time. However, the incidence rate of PN Chemotherapy-induced Peripheral Neuropathy (CiPN) of serious adverse reactions such as is increasing post-treatment. It is reported that the incidence Bortezomib-induced Peripheral Neuropathy (BiPN) is 40% to 60% [1-5]. The incidence of Thalidomide-induced Peripheral Neuropathy (TiPN) is 25% to 75% [6]. Currently, there is no specific therapeutic drug for MM CiPN. It primarily depends on adjusting the drug dose, administration time, and administration mode to reduce the incidence and severity of PN. Moreover, it will inevitably affect the efficacy of MM chemotherapy. It is possible to repair nerve injury with timely giving B vitamins (Mecobalamin, B1, B6), nerve growth factor, and other neuroprotective agents. Patients with MM often have to limit the dose of therapeutic drugs, reduce the course of treatment, or even discontinue taking drugs as they cannot tolerate Peripheral Neuropathy (PN) [7]. PN largely affects the clinical application and efficacy of drugs. Therefore, how to effectively prevent and treat MM CiPN is the key problem to improve the quality of life and prolong the survival time of patients with MM. The book Inner Canon of Huangdi published acupuncture and moxibustion for the first time during the Warring States period. They have been widely used owing to their wide adaptability, easy operation, immediate therapeutic effect, low cost, and few side effects. Acupuncture and moxibustion can stimulate receptors or cause regular discharge of nerve fibers, lead to activation of peripheral nerve and central nervous system, and release of various neurotransmitters [8]. The specific effect of acupuncture depends on the choice of acupuncture location, form and duration of stimulation, and treatment method [9]. An abstruse part of Traditional Chinese Medicine (TCM) acupuncture is midnight-noon ebb-flow. It indicates that under the influence of climate change and natural time, human functional activities and pathological changes have certain laws. Midnight-noon ebb-flow is an ancient treatment technique based on the five acupoints of Jing, Xing, Shu, Jing, and He that is collectively called Five-shu points combined with the Five Elements and Yin and Yang. It is quite similar to the biological rhythm-based time medicine rising at home and abroad in recent years. It is representative of the chronomedicine of TCM. Its scientific value has gained attention, and its unique clinical efficacy is recognized worldwide. Meridian flow acupuncture is a model of the combination of acupuncture and chronomedicine. This treatment technique is widely used in clinical practice. It treats a variety of diseases, particularly useful in treating pain. Some clinical trials have confirmed that acupuncture has an effective PN for diabetes, Human Immunodeficiency Virus (HIV), herpes zoster, and diseases with unknown causes [8,10-12]. Clinical trials at different foreign centers have also demonstrated that acupuncture and moxibustion have a potential curative effect on alleviating tumor neuralgia [13,14]. Moreover, acupuncture and moxibustion have achieved a curative effect in the treatment of Chemotherapy-Related Peripheral Neuropathy (CiPN) [15], and other studies have shown that acupuncture and moxibustion can improve the nerve conduction velocity of peripheral neuropathy [16]. A single group of case studies demonstrated that the clinical

manifestations and symptoms of patients with BiPN were improved after receiving acupuncture and moxibustion [17,18]. The above research depicts that acupuncture and moxibustion have great potential in the treatment of PN caused by chemotherapy. Therefore, we included MM chemotherapy-related patients with PN who were hospitalized in the Hematology Department of our hospital from September 2018 to May 2021 and fulfilled the inclusion criteria as the study participants, designed a randomized controlled study, and comprehensively evaluated the patients' PN using a Visual Analog Scale (VAS) pain score, Functional Assessment of Cancer Therapy Neurotoxicity (FACT/GOG-NTx) neurotoxicity rating scale, and Nerve Conduction Velocity (NCV), to observe the efficacy and safety of midnight-noon ebb-flow acupuncture combined with mecobalamin for the treatment of MM CiPN.

Materials and Methods

Patient information

Patients with MM (unlimited type and stage) hospitalized for chemotherapy at our center from September 2018 to May 2021 were enrolled in the study. The treatment group (19 cases), aged 50 to 72 years, with a median age of 57 years; the control group (20 cases),

Table 1: Patient characteristics.

	Treatment group	Control group
Number (patients)	19	20
Male	11	14
Female	8	6
Naive (N)	10	12
Relapse/refractory (N)	9	8
Medium age (year)	57.3	59
Clinical stage (N)		
DS stage		
IIA	2	1
IIB	0	0
IIIA	13	15
IIIB	4	4
ISS stage		
I	1	1
II	6	6
III	12	13
M protein(N)		
IgG	10	11
IgA	4	3
IgM	0	0
IgD	2	1
Klight chain	1	2
Alight chain	2	3
Mean bone marrow plasma cells (%)	31.7	37.3
Mean hemoglobin (g/L)	86.3	88.5
PN grade (CTCAE)		
G2	5	4
G3	10	12
G4	4	4

aged 53 to 75 years, with a median age of 59 years. There was no significant difference between the two groups (Table 1).

Inclusion criteria: 1. Patients diagnosed with MM; 2. Patients without PN at baseline, those experiencing PN grade 2 or above after Bortezomib chemotherapy (the severity of neuropathy was evaluated according to NCI CTCAE, version 3.0); Electromyography examination suggesting conduction disorders of the median and peroneal nerves, slowing down of one item or more items of NCV; 3. Willing to terminate chemotherapy for three months and receive treatment using this method; Patients who signed informed consent.

Exclusion criteria: 1. Patients who were pregnant; 2. Those with severe heart, liver, and kidney dysfunction or other critical diseases (such as malignant tumors); 3. Those with PN caused by reasons other than chemotherapy, such as plasma cell tumor compression, nutritional disorders, and infection; 4. Those with platelet count $<30 \times 10^9/L$ and white blood cell count $<3.0 \times 10^9/L$ before the treatment; 5. Patients who were unable to communicate due to severe cognitive disorder; 6. Those who did not cooperate or refused to sign informed consent.

Excluding and withdrawing criteria: 1) Patients with worsened, deteriorated or severe adverse reaction; 2) Those with treatment intolerance and withdrawal from treatment group; 3) Those receiving a combination of the drug affecting efficacy and safety of the trial; 4) Those who were lost to follow-up. Forty-four patients who fulfilled the inclusion and exclusion criteria were randomly divided into two groups, including 22 cases in the treatment group treated with acupuncture combined with mecobalamin and 22 cases in the control group treated with mecobalamin alone. The follow-up time was four cycles. In the treatment group, one case underwent autologous stem cell transplantation, one case died, and another case was lost to follow-up; in the control group, one case was lost to follow-up, while another case died of severe pneumonia. Except for patients who withdrew from the study, 20 cases in the control group and 19 cases in the treatment group were included in the statistics. There was no significant difference in age, sex, PN grade, VAS score, and FACT/GOG-Ntx score between the two groups before treatment.

Therapeutic method

Forty-four patients who met the inclusion criteria were randomly divided into two groups. Total 39 cases in the control and treatment groups were effective. (1) 20 cases in the methylcobalamin group

(control group): 1000 μ g methylcobalamin was injected intravenously once daily, 10 times and thereafter 500 μ g orally three times a day. (2) 19 cases in midnight-noon ebb-flow acupuncture combined with methylcobalamin group (treatment group): Acupuncture treatment was added based on the treatment in the control group. The acupuncture scheme was identified and popularized by the State Administration of traditional Chinese medicine in 2004. The acupuncture parts were as follows Zusanli (ST36), Fenglong (ST40), Sanyinjiao (SP6), Shangqiu (SP5), Shenmen (HT7), Tongli (HT5), Wangu (SI4), Feiyang (BL58), Taixi (KI3), Zhaohai (KI6), Neiguan (PC6), Waiguan (SJ5), Zulinqi (GB41), Yanglingquan (GB34), Taichong (LR3), Xingjian (LR2), Chize (LU5), and Yuji (LU10). Acupuncture method: It includes routinely disinfecting using 75% alcohol, and vertically inserting 28 1.312335958-inch Huatuo acupuncture needles under the skin. Each acupoint is inserted into 0.656167979004 inches, and then the manipulation is implemented. Pull out the needle quickly without twirling. The frequency of treatment is three times a week. The course of treatment is four weeks. Continuous treatment of four courses is needed.

Evaluation criteria of curative effect of peripheral neuropathy

(1) FACT/GOG-Ntx subscale (neurotoxicity assessment tool) (Table 2), send out a questionnaire survey on patients' daily activity ability [19], evaluate the degree of neuropathy, and evaluate neuralgia using VAS pain score (Table 3) [20]. (2) Before and after treatment, professional technicians were responsible for the measurement of nerve conduction velocity. The Motor Conduction Velocity (MCV) of the bilateral median and common peroneal nerves were recorded using skin surface electrodes, and the average value was recorded. Moreover, Sensory Conduction Velocity (SCV) of the bilateral median and sural nerves.

Statistical analysis

SPSS20.0 software was used to statistically analyze the data, and the quantitative data in line with normal distribution were analyzed. Mean \pm standard deviation ($x \pm s$) indicates that paired t-test is used for comparison before and after treatment, and two independent sample t-test is used for comparison between the two groups. A nonparametric test was used for quantitative data with non-normal distribution; the Chi-square test of counting data, $P < 0.05$, the difference was statistically significant.

Table 2: FACT/GOG—Ntx neurotoxicity assessment tool.

Symptoms	Grade				
	0	1	2	3	4
Numbness or tingling in the hand	0	1	2	3	4
Numbness or tingling in feet and hands	0	1	2	3	4
Hands feel uncomfortable	0	1	2	3	4
Feet feel uncomfortable	0	1	2	3	4
Arthralgia or muscle spasm	0	1	2	3	4
Feeling weak	0	1	2	3	4
Hearing difficulties	0	1	2	3	4
Tinnitus	0	1	2	3	4
Button difficulty	0	1	2	3	4
Unable to distinguish the shape of small objects in your hand	0	1	2	3	4
Walking difficulty	0	1	2	3	4

0: Not at all; 1: Slight; 2: Obvious; 3: Quite obvious; 4: Very serious

Results

The comparison of peripheral neuropathy evaluation indices (VAS pain score, FACT/GOG-Ntx quality of life questionnaire scores, and NCV) with patients in the control group (mecobalamin) and treatment group (mecobalamin + acupuncture) is demonstrated in Table 4. The results show that there is no difference in the evaluation indices of PN between the two groups before treatment. It was statistically significant ($P>0.05$) and comparable between the two groups. The comparison of peripheral neuropathy evaluation indices (VAS pain score, FACT/GOG-Ntx quality of life questionnaire scores, and NCV) with patients in the treatment group (mecobalamin + acupuncture) is shown in Table 5. The results showed that the VAS score and the FACT/GOG-Ntx score were significantly lower than that before treatment, SCV and MCV were higher than that before treatment, indicating that the symptoms of PN in the treatment group were significantly improved. The statistical results showed that the evaluation indices of PN in the treatment group were different before and after treatment with statistically significant (all $P<0.05$). The comparison of peripheral neuropathy evaluation indices (VAS pain score, FACT/GOG-Ntx quality of life questionnaire scores, and NCV) with patients in the control group (mecobalamin) is shown in Table 6. The results showed that the VAS pain score and FACT/GOG-Ntx of patients in the control group after four weeks of mecobalamin treatment were lower than that before treatment, and SCV and MCV were higher than that before treatment, indicating that the symptoms of PN in the control group were improved. The statistical results showed that there was a significant difference in the evaluation indices

of PN in the control group before and after treatment (all $P<0.05$). The comparison of peripheral neuropathy evaluation indices (VAS pain score, FACT/GOG-Ntx quality of life questionnaire scores, and NCV) after four cycles of treatment with patients in the treatment group (mecobalamin + acupuncture) and control group (mecobalamin) is shown in Table 7. The results showed that the improvement of PN in the treatment group (mecobalamin + acupuncture) was superior to that in the control group (mecobalamin). There were significant differences in VAS score, FACT/GOG-Ntx score, and NCV between the two groups ($P<0.05$).

Discussion

TCM believes that CiPN is mainly related to deficiency and blood stasis of the body, which is highly similar to the "stiff" of TCM and is closely related to Qi deficiency, blood stasis, and turbid phlegm [21]. The primary pathogenesis of the disease is Yin deficiency and blood stasis. The deficiency indicates Qi and Yin deficiencies, while blood stasis signifies blocking collaterals. Moreover, blood stasis is caused by deficiency. Deficiency is the foundation, while blood stasis is the standard. Both are combined and run through CiPN. Acupuncture and moxibustion can relax blood vessels, enhance blood perfusion, and improve symptoms [22,23]. The clinical symptoms of CiPN include affecting the sensory, motor, and autonomic nerves. In general, the long nerve fibers of the limbs are involved first, resulting in neuropathy at the limb ends, which is distributed symmetrically like hand and foot garters. During chemotherapy, there will be numbness, paresthesia, and hypersensitivity of fingers and toes, such as numbness, tingling, and so on. It is related to the changes

Table 3: VAS Pain scoring criteria (Score 0–10).

0	It does not hurt at all
Below 3	There is pain and can bear it
4–6	The patient suffered pain and affected sleep, which was tolerable
7–10	The patient has gradually intense pain, which is unbearable, affecting appetite and sleep

Table 4: Comparison of evaluation indices of peripheral neuropathy between the two groups before treatment.

Index	Control group	Treatment group	p-value
VAS pain score	5.55 ± 1.830	5.47 ± 2.256	0.910
FACT/GOG-Ntx score	18.5 ± 2.439	17.63 ± 3.542	0.389
Sensory nerve conduction velocity (m/s)			
Median nerve	42.66 ± 3.312	42.51 ± 3.408	0.897
Sural nerve	38.98 ± 2.160	39.91 ± 3.014	0.286
Motor nerve conduction velocity (m/s)			
Median nerve	46.95 ± 2.227	48.11 ± 2.746	0.167
Common peroneal nerve	41.23 ± 1.966	42.27 ± 2.046	0.120

Table 5: Comparison of evaluation indexes of peripheral neuropathy in the treatment group before and after treatment.

Index	Before treatment	After treatment	p-value
	5.47 ± 2.256	3.05 ± 1.234	<0.05
FACT/GOG-Ntx score	17.63 ± 3.542	13.31 ± 2.472	<0.05
Sensory nerve conduction velocity (m/s)			
Median nerve	42.51 ± 3.408	47.34 ± 1.783	<0.05
Sural nerve	39.91 ± 3.014	43.58 ± 2.887	<0.05
Motor nerve conduction velocity (m/s)			
Median nerve	48.11 ± 2.746	51.45 ± 2.365	<0.05
Common peroneal nerve	42.27 ± 2.046	45.24 ± 1.584	<0.05

Table 6: Comparison of evaluation indices of peripheral neuropathy in the control group before and after treatment.

Index	Before treatment	After treatment	p-value
VAS pain score	5.55 ± 1.830	4.10 ± 0.995	<0.05
FACT/GOG-Ntx score	18.5 ± 2.439	16.40 ± 1.772	<0.05
Sensory nerve conduction velocity (m/s)			
Median nerve	42.66 ± 3.312	45.45 ± 2.548	<0.05
Sural nerve	38.98 ± 2.160	40.91 ± 2.126	<0.05
Motor nerve conduction velocity (m/s)			
Median nerve	46.95 ± 2.227	49.04 ± 2.186	<0.05
Common peroneal nerve	41.23 ± 1.966	42.92 ± 1.739	<0.05

Table 7: Comparison of evaluation indexes of peripheral neuropathy between the two groups after treatment.

Index	Control group	Treatment group	p-value
VAS pain score	4.10 ± 0.995	3.05 ± 1.234	<0.05
FACT/GOG-Ntx score	16.40 ± 1.772	13.31 ± 2.472	<0.05
Sensory nerve conduction velocity (m/s)			
Median nerve	45.45 ± 2.548	47.34 ± 1.783	<0.05
Sural nerve	40.91 ± 2.126	43.58 ± 2.887	<0.05
Motor nerve conduction velocity (m/s)			
Median nerve	49.04 ± 2.186	51.45 ± 2.365	<0.05
Common peroneal nerve	42.92 ± 1.739	45.24 ± 1.584	<0.05

in cold and heat. The pain is limited to the toes and soles of the feet; however, it will also involve the fingers and palms. Severe BiPN and TiPN will cause loss of reflex and proprioception, resulting in ataxia and gait disorder. Motor neuropathy is rare, primarily manifested as muscle convulsion, tremors, and distal muscle weakness. Decreased muscle strength of hand and foot muscles will affect fine movements, such as writing, turning keys, and unstable standing. Autonomic neuropathy can further lead to orthostatic hypotension, bradycardia, sexual dysfunction, and constipation. The pathological mechanism of BiPN may be as follows: (1) bortezomib acts on the cytoplasm of dorsal root ganglion and produces toxic effects, resulting in the disorder of neuronal transcription, translation, and transport; (2) Promote the release of calcium in the endoplasmic reticulum and induce mitochondria to regulate cell apoptosis; (3) Bortezomib can simultaneously inhibit the transcription of nerve growth and genetic factors [24], and the level of nerve growth factor is closely related to the severity of BiPN [25]. Animal studies have pointed out that after acupuncture treatment, the protein and neurotrophic factor mRNA levels of dorsal root ganglion can rise [26]. Our study shows that acupuncture combined with mecobalamin can significantly reduce VAS pain score and FACT/GOG-Ntx quality of life score of patients with MM CiPN, improve NCV, and improve PN better than mecobalamin alone. There was no infection at the puncture site or bleeding and other side effects in the treatment group. This depicts that acupuncture is a safe and effective treatment for CiPN in patients with MM.

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