ORIGINAL RESEARCH

Quma Tongluo Prescription in the Treatment of Chronic Oxaliplatin Related Peripheral Neuropathy: A Single-Center, Open, Randomized Controlled Study

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ABSTRACT

Objective • To observe the effect of oral Quma Tongluo decoction on oxaliplatin-related chronic peripheral neuropathy.

Methods • A total of 64 patients who met the inclusion criteria were randomly divided into an experimental group and a control group, with 32 cases in each group. The experimental group took Quma Tongluo decoction granules orally (2 times a day, 1 package each time, morning and evening after meals), and the control group took mecobalamin tablets orally (1 tablet each time, 3 times a day, after meals). After 4 weeks of treatment, the quantitative score of chronic peripheral neuropathy severity, a quantitative score of numbness, a quantitative score of pain, a chemotherapeutic peripheral neurotoxicity score, comprehensive neuropathy score, peripheral neurotoxicity grade, KPS score, and neuropathy area range score were compared between the two groups before and after treatment.

Results • Before treatment, there were no significant differences between the two groups in the quantitative score of chronic peripheral neuropathy severity, quantitative score of numbness, chemotherapeutic peripheral neurotoxicity score, total neuropathy score, peripheral neurotoxicity grade, and chronic OIPN symptom range score ($P > .05$). After 4 weeks of treatment, there were significant differences in the quantitative score of chronic peripheral neuropathy severity, quantitative score of numbness, chemotherapeutic peripheral neurotoxicity score, total neuropathy score, peripheral neurotoxicity grade, and chronic OIPN symptom range score between the two groups ($P < .05$). There was no significant difference in pain quantification score and KPS score between the two groups before and after treatment ($P > .05$). The total effective rate of Quma Tongluo decoction in the treatment of oxaliplatin-related chronic peripheral neuropathy was higher than that of mecobalamin (87.1% > 20.6%), and no obvious adverse reactions such as Gastrointestinal reactions and allergic reactions were observed.One patient in the experimental group had diarrhea, the incidence of adverse reactions was about 3.2%, and the control group had no adverse reactions.

Conclusions • Quma Tongluo decoction can effectively treat oxaliplatin-related chronic peripheral neuropathy, reduce the symptoms while reducing the scope of symptoms, and has no obvious adverse reactions in clinical practice, with good safety. (*Altern Ther Health Med.* 2025;31(1):134-142).

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INTRODUCTION

Colorectal cancer is the third most common cancer in China which incidence was 12.2%[1], and its incidence is still increasing with the improvement of residents' living standards and the change of dietary structure.[2] Oxaliplatin, as a third-generation platinum-based broad-spectrum chemotherapeutic agent, is widely used in the clinical chemotherapy of patients with colorectal cancer. Peripheral nerve neurotoxicity caused by oxaliplatin is extremely common. OIPN was occurs in above 85% patients after treatment of oxaliplatin.[3]

Oxaliplatin-induced peripheral neuropathy (OIPN) can be divided into can be divided into two distinct forms, acute and chronic, according to the incidence, symptoms, duration, mechanisms, and other clinical features. Acute OIPN,occurs in 85–96% of patients within hours of infusion, is self-limited and can disappear completely within 7 days after drug withdrawal. It is characterized by cold-sensitive peripheral paresthesia (hands and feet dysesthesia and paresthesia) and motor symptoms.The incidence of chronic OIPN is 40–93%, which always occur at cumulative doses exceeding 780–850 mg/m^2.[4]

The recovery of chronic OIPN is slow. The symptoms of some patients can be alleviated with time, however, the majority of patients will still experience irreversible neurological damage, which may persist for years or even life after chemotherapy.[5] Chronic OIPN mainly damages sensory nerves but also can damage motor nerves and autonomic nerves. Clinically, chronic OIPN can lead to sensation loss and changes in proprioception. The symptoms of chronic OIPN are characterized by persistent numbness, pain, and paresthesia of the hands and feet, and a characteristic "electric shock" sensation after touching cold water or metal, which is distributed in a "sock" or "glove" distribution and can progress to the proximal end. In the later stage, decreased vibration perception, slow proprioception, and fine sensorimotor disorders may occur.[6-8] It not only adversely affects the quality of life of patients but also reduces the compliance of patients with chemotherapy, leading to dose reduction or chemotherapy interruption, which inevitably reduces the efficacy of chemotherapy and increases the risk of tumor recurrence and metastasis, thereby endangering the survival of patients. [9-14]

Currently, a safe and effective prevention and treatment system has not been established in modern Medicine. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update indicate that there is currently no way to prevent CIPN, and duloxetine is the only drug recommended by the American Society of Clinical Oncology (ASCO) for the treatment of OIPN.In the clinical treatment of chronic OIPN, most of the patients are treated with neurotrophic drugs based on diabetic peripheral neuropathy, but the efficacy is often not satisfactory.[7] Traditional Chinese Medicine has shown a unique therapeutic effect in the treatment of chemotherapy-induced peripheral neuropathy, with fewer side effects than Western Medicine, and has great research potential.[15-20] TMs appear to be effective and safe in the prevention of chronic OIPN, especially severe chronic OIPN. [21]Professor Hou Fenggang is the chief physician and postdoctoral supervisor of the Department of Oncology at Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine. He has been engaged in clinical research on the prevention and treatment of gastrointestinal tumors with integrated traditional Chinese and Western Medicine for a long time. He applied Quma Tongluo prescription in the treatment of chronic OIPN in long-term clinical treatment and achieved good results.Therefore, this study aims to observe the clinical efficacy and safety of Quma Tongluo prescription in the treatment of chronic OIPN.

METHODS

Subjects

Patients with colorectal cancer diagnosed as oxaliplatin-related chronic peripheral neuropathy in the Third Department of Oncology, Shanghai Traditional Chinese Medicine Hospital, from June 2022 to February 2023, were selected as the study subjects. This study was approved and filed by the Medical Ethics Committee of Shanghai Traditional Chinese Medicine Hospital, and all patients signed the informed consent.

Diagnostic criteria

The diagnostic criteria for chronic OIPN were based on chemotherapy-induced peripheral neuropathy, oxaliplatin-specific Levi sensory neurotoxicity grading, peripheral neuritis in Neurology, and clinical features of acute and chronic OIPN: (1) Symptoms: After the previous use of oxaliplatin-containing chemotherapy regimens (such as FOLFOX/XELOX, etc.), the patient had characteristic "electric shock" paesthesia after touching cold water and metal, and appeared "glove" and "sock" symmetrical distribution of sensory nerve damage such as numbness and pain, and the symptoms could not be relieved and disappeared within 7 days after the complete withdrawal of the drug. It may be accompanied by weakness of hands and feet, fine motor disorders (such as buttons, writing, etc.), and other partial motor nerve function damage symptoms. Peripheral neuropathy caused by other factors (such as diabetes mellitus, vascular disease, cervical and lumbar disc herniation, Parkinson's disease, etc.) was excluded. (2) Signs: weakened needle sensation, weakened vibration sensation, decreased muscle strength, weakened or lost tendon reflex, or accompanied by dysfunction. (3) Electromyography: prolonged latency of sensory and motor nerve conduction potential, decreased amplitude, and slowed sensory nerve conduction velocity.

Screening Criteria

Inclusion. (1) Age>18 years old, regardless of gender; (2) Colorectal cancer diagnosed by histopathology; (3) patients with oxaliplatin-induced chronic peripheral neuropathy (referring to the diagnostic criteria of chronic OIPN) after the application of oxaliplatin-containing chemotherapy (XELOX/FOLFOX, etc.); (4) patients with no intellectual and mental disorders, normal language expression ability, the ability to judge their own pain and numbness and other symptoms and general conditions, and cooperative evaluation; (5) Kamofsky Performance Status (KPS) score ≥60; (6) Predicted survival time >3 months; (7) Patients agreed to receive the treatment and signed the informed consent.

Exclusion. (1) Patients receiving other chemotherapeutic agents that may cause peripheral neuropathy or hand-foot syndrome; (2) patients with peripheral neuropathy (mainly pain and numbness) caused by diabetes, poisoning, vascular disease, nervous system disease, and other factors before chemotherapy or at the time of enrollment; (3) patients with severe organic damage of heart, liver, brain, kidney and hematopoietic dysfunction of bone marrow; (4) patients with severe pain in other parts of the body; (5) patients with hand and foot ulcers or skin infections; (6) patients who are participating in other clinical trials.

Drop out criteria. (1) Patients with poor compliance, unable to adhere to the treatment and voluntarily asked to withdraw; (2) Unable to continue the trial due to serious

adverse events or adverse reactions; (3) The patient's condition changed suddenly during the treatment, which affected and interfered the researcher; (4) patients who did not take medication as planned after enrollment and whose efficacy could not be determined.

Treatment

Experimental group. Quma Tongluo formula is a personal experience formula used by chief physician Hou Fenggang in a large number of clinical practices. In the early clinical observation, this formula has a good therapeutic effect on chronic OIPN, so it is pretended to be the Chinese medicine group in this study.

After enrollment, patients were treated with Quma Tongluo decoction granules (2 times a day, 1 package each time, morning and evening after meals) for 28 days. The composition of Quma Tongluo prescription is Caulis spatholobi 30 g, large-leaved gentian 18 g, silkworm excrement 18 g, centipede 3 g. Jiangyin Tianjiang Pharmaceutical Industry made Chinese medicine granules, and 1 pack of Chinese Medicine was made into 2 packets of granules.

Control group. Mecobalamine belongs to endogenous vitamin B12 and is a commonly used neurotrophic drug in clinic. Mecobalamine can improve lipid and protein metabolism, provide favorable conditions for neuronal myelination and nerve axon regeneration, repair damaged neurons and tissues, improve nerve conduction speed, and improve limb pain, numbness and other symptoms of patients.

Mecobalamin tablets (1 tablet each time, 3 times a day, after meals) were taken for 28 days after enrollment. Mecobalamin Tablets (Eisai China Inc, Specification:0.5 mg, Chinese Medicine approval number H20143107).

Administration of Medications

After the first assessment, the enrolled patients were given the medication for 28 days, and the patients were informed about the method of taking the medication. During the medication period, patients should record the medication schedule card every day, clearly record the medication date, and communicate with the researchers in time if they stop or reduce the dose by themselves.

Indicators of observation

Quantitative score of chronic peripheral neuropathy severity. The chronic OIPN severity score is a comprehensive score based on the degree and range of paresthesia, such as numbness and pain, and the degree of motor function limitation of chronic OIPN. Numeric grading was used: numbers from 0 to 10 represented different levels of symptoms, with 0 being asymptomatic and 10 being the most severe symptom, and patients were asked to circle a number that best represented the severity of their symptoms. (1-3.5 was mild, 3.6-6.5 was moderate, and 6.6-10 was severe). The average score of the degree of comprehensive symptoms in the past 7 days was marked. The scores were scored once before and after treatment.

Quantitative score of numbness. Numbness is graded numerically: a number from 0 to 10 represents different degrees of numbness, 0 indicates no numbness, 10 indicates the most severe numbness, the higher the score, the more severe numbness, and the patient is asked to circle the number that best represents numbness. (1 to 3.5 is mild, 3.6 to 6.5 is moderate, and 6.6 to 10 is severe). Mark the most severe symptom severity score in the previous 24 hours. Score was performed before and after treatment.

Quantitative pain score. Pain levels are graded numerically: a number from 0 to 10 represents different pain levels, 0 being no pain, 10 being the most severe pain, the higher the score the more severe the pain, and the patient is asked to circle the number that best represents the pain level. (1 to 3.5 is mild, 3.6 to 6.5 is moderate, and 6.6 to 10 is severe). Mark the most severe symptom severity score in the previous 24 hours. Score was performed before and after treatment.

Chemotherapeutic peripheral neurotoxicity score. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EQLE) is a tool for patients to self-assess chemotherapy-induced peripheral nerve injury, and is one of the widely used CIPN self-assessment scales. It was used to evaluate the symptoms and functional limitations of peripheral neuropathy in cancer patients, including 3 scales of sensory, motor and autonomic nerve damage, with a total of 20 items. The scale adopts Likert 4-level scoring method, with 1 to 4 points for each item, where 1 means "not at all" and 4 means "very", and the higher the score, the more severe the symptoms.

The EORTC QLQ-CIPN 20 chemotherapeutic peripheral neurotoxicity scale developed by the European Organization for Research and Treatment of Cancer was used to reflect the severity of chronic OIPN, with higher scores indicating more severe symptoms. The scores were scored once before and after treatment.

Grading of peripheral neurotoxicity. The CIPN grading criteria were selected as WHO grading criteria for peripheral nerve toxicity of anticancer drugs (World Health Organi-zation Scale). This grading standard was developed by WHO in the 1970s. The evaluation of peripheral neuropathy mainly includes the degree of damage of sensory nerve, motor nerve and deep tendon reflex, which is divided into 0-4 grades. The higher the grade, the more severe the nerve damage caused by chemotherapy. Grade 0 is normal. Grade 1: mild, transient paresthesia, hypoesthesia or hypoesthesia of tendon reflexes. Grade 2: moderate objective sensory loss or abnormality, mild weakness. Grade 3: muscle and tendon paresthesia affects the function of the limbs, and the limbs are unresponsive or even lost, which seriously leads to motor dysfunction. Grade 4: Paralysis. The scores were scored once before and after treatment.

Total neuropathy score. The total neuropathy score (TNS) is a comprehensive assessment of peripheral nerve function based on subjective motor, sensory and autonomic symptoms, combined with objective muscle strength, tendon reflex, vibration, quantified vibration, quantified temperature and nerve conduction tests. It is a neurological status

assessment tool that integrates subjective symptoms and objective examination of patients, and is widely used in the assessment of chemotherapy-mediated peripheral neuropathy, which can well reflect the severity and disease changes of CIPN. TNSc (total neuropathy scoreclinical, TNS-c) is a clinical version of the Total neuropathy score excluding nerve conduction and quantitative sensory tests.TNS has 11 scoring items, and each item is divided into 5 levels, corresponding to 0 to 4 points, and the sum of the scores of each item is the total score (0 to 44 points). The higher the total score, the more serious the symptoms of peripheral nerve dysfunction.

The TNSc scale, the clinical version of the total neuropathy score, was used to assess peripheral neuropathy, and the higher the total score, the more severe the neuropathy. The scores were scored once before and after treatment.

Chronic OIPN symptom range score. At present, there is no evaluation system for the symptom range of chronic OIPN. Combined with the clinical symptoms of patients, the scoring criteria are formulated for preliminary evaluation of the symptom range: 1 point is for 1 finger joint, 1 point is for 1 toe, 1 point is for 1/2 palm area, 1 point is for 1/3 plantar area, 1 point is for small arm, and 1 point is for the lower leg. The score was 5 points for all hands and 4 points for all feet. If the range of numbness and pain was 2 finger joints and toes, the range score was 3 points. 3 finger joints, toes, and the area of the front 1/3 of the sole of the foot were rated as 5 points. The difference between the pre-treatment range score and the post-treatment range score could represent the extent of symptom relief in patients with chronic OIPN. The scores were scored once before and after treatment.

KPS score. Karnofsky Performance Status (Karnofsky Performance Status) is a standard used to measure a patient's physical functioning. Specific applications include assessing a patient's quality of life and tolerance to the side effects of treatment. It is often used to evaluate the prognosis and treatment effect of cancer patients. More than 80 points is non-dependent (independent), that is, self-care level. 50 ~ 70 is divided into semi-independent (semi-independent), that is, life is semi-independent. A score below 50 is considered dependent, meaning you need help to live your life.

Using the KPS scoring standard, a higher KPS functional status score indicates better health status and better tolerance to side effects caused by chemotherapy. The scores were scored once before and after treatment.

Efficacy evaluation criteria

The Nimodipine method was used for scoring: (total score before treatment - total score after treatment)/ total score before treatment × 100%.Take quantitative score of chronic peripheral neuropathy severityas the main index of calculating efficiency.

The efficacy was determined according to the standard of "Guiding Principles for Clinical Research of New Chinese Medicine": clinical recovery: clinical symptoms and signs disappeared or basically disappeared, and the syndrome score reduced by ≥ 90%. Significant effect: clinical symptoms and signs were significantly improved, and the syndrome score was reduced by ≥ 70%. Effective: the clinical symptoms and signs were improved, and the syndrome score was reduced by ≥ 30%. Ineffective: the clinical symptoms and signs were not significantly improved or even aggravated, and the syndrome score was reduced by ≤ 30%. Aggravation: the clinical symptoms and signs were aggravated, and the syndrome score decreased ≤0.

Statistical analysis

Statistic Package for Social Science (SPSS) 25.0 was used for statistical analysis. The normal data were described by mean ± standard deviation ($\bar{x} \pm s$), and the skewed data were described by median (P_{25}, P_{75}). Two independent sample t-tests compared normal measurement data, non-normal data were compared by rank sum test or Fisher's test, count data were compared by chi-square test or Fisher's exact probability method, $P < .05$ was considered statistically significant, $P < .01$ was considered statistically significant.

RESULTS

General Information

A total of 64 patients with colorectal cancer who had previously used oxaliplatin-based chemotherapy were enrolled in this study. According to the digital random table method, they were randomly divided into the experimental group and the control group, with 32 cases in each group. There were 20 males and 11 females in the experimental group. The oldest was 79 years old, and the youngest was 42 years old, with an average of (65.16±8.89) years old. There were 21 cases of colonic malignant tumors and 10 cases of rectal malignant tumors. There were 15 males and 14 females in the control group. The oldest was 78 years old, and the youngest was 24 years old, with an average of (60.21±13.17) years old. There were 18 cases of colonic malignant tumors and 11 cases of rectal malignant tumors. The average cumulative dose of OXA was (1302.90±316.19) mg in the experimental group and (1394.48±488.32) mg in the control group. There was no significant difference in general conditions between the two groups ($P > .05$), and the two groups were balanced and comparable.See Table 1.

Table 1.Basic data of two groups of patients

General information	Experimental group	Control group	*t*	*P* value
sex				
male	20	15	1.009	.315
female	11	14		
age	(65.16±8.89)	(60.21±13.17)	1.718	.091
diagnosis				
Rectal cancer	10	11	0.212	.645
Colon cancer	21	18		
Pathological classification				
adenocarcinoma	30	28	/	.000
unknown	1	1		
Degree of differentiation				
Poorly differentiated	7	12	/	.274
Moderately differentiated	20	14		
unknown	4	3		
Clinical stage				
I	2	1	/	.310
II	10	4		
III	13	19		
IV	1	2		
unknown	5	3		

Comparison of quantitative scores of chronic peripheral neuropathy severity

Intra-group comparison: the overall severity scores of chronic OIPN after treatment were significantly different from those before treatment in both groups ($P < .01$). There was no significant difference in the overall severity score of chronic OIPN between the two groups before treatment ($P > .05$). After treatment, the overall severity score of OIPN in the experimental group was significantly lower than that in the control group ($P < .01$), and the difference of the overall severity score of OIPN before and after treatment in the experimental group was higher than that in the control group ($P < .01$). See Table 2.

Table 2. Quantitative score of chronic peripheral neuropathy severity before and after treatment (M (P_{25}, P_{75}))

Group	Number of cases	Before treatment	After treatment	Difference	Effective rate
Experimental Group	31	7 (6, 8)	2 (1, 3)[a,c]	5 (3,6)[b]	87.1%
Control Group	29	7 (6, 8)	6 (4, 7)[a]	1 (1,2)	20.6%

[a]Compared with this group before treatment, $P < .01$
[b]Compared with control group, $P < .01$
[c]Compared with the control group after treatment, $P < .01$

Quantitative score of numbness

Intra-group comparison: the numbness scores of the two groups after treatment were significantly different from those before treatment ($P < 0.01$).

There was no significant difference in numbness score between the two groups before treatment ($P > .05$). After treatment, the numbness score of the experimental group was significantly lower than that of the control group ($P < .01$), and the difference of numbness score before and after treatment in the experimental group was higher than that in the control group ($P < .01$). See Table 3.

Table 3. Quantitative score of numbness before and after treatment (M (P_{25}, P_{75}))

Group	Number of cases	Before treatment	After treatment	Difference
Experimental Group	31	7 (6,8)	2 (1,3)[a,c]	5 (3,6)[b]
Control Group	29	7 (5.5,8)	6 (3.5,7)[a]	1 (1,2)

[a]Compared with this group before treatment, $P < .01$
[b]Compared with control group, $P < .01$
[c]Compared with the control group after treatment, $P < .01$

Quantitative pain score

Intra-group comparison: the pain scores of the two groups after treatment were significantly different from those before treatment ($P < .01$). There was no significant difference in the pain scores before and after treatment between the two groups ($P > .05$). See Table 4.

Table 4. Quantitative score of pain before and after treatment (M (P_{25}, P_{75}))

Group	Number of cases	Before treatment	After treatment	Difference
Experimental Group	31	1 (0,1)	0 (0,0)[a]	0 (0,1)
Control Group	29	1 (0,1)	0 (0,1)[a]	0 (0,1)

[a]Compared with this group before treatment, $P < .01$.

Chemotherapy peripheral nerve toxicity score (CIPN 20)

Intra-group comparison: The CIPN score of the two groups after treatment was significantly different from that before treatment ($P < 0.01$).

Inter-group comparison: there was no significant difference in CIPN score between the two groups before treatment ($P > 0.05$). After treatment, the CIPN score of the experimental group was lower than that of the control group ($P < 0.01$), and the CIPN score difference of the experimental group before and after treatment was higher than that of the control group ($P < 0.01$). See Table 5.

Table 5. CIPN score before and after treatment (M (P_{25}, P_{75}))

Group	Number of cases	Before treatment	After treatment	Difference
Experimental Group	31	30 (28,33)	24 (23,27)[a,c]	5 (3,9)[b]
Control Group	29	30 (28,33.5)	28 (25.5, 32.5)[a]	2 (1.5,4)

[a]Compared with this group before treatment, $P < .01$
[b]Compared with control group, $P < .01$
[c]Compared with the control group after treatment, < .01

Grading of peripheral neurotoxicity

Before treatment, chronic OIPN was mainly distributed in grade 2 and grade 3 in the two groups, and there was no significant difference in the grade of peripheral neurotoxicity between the two groups ($P > .05$). After treatment, in terms of the distribution of chronic OIPN neurotoxicity grades, the experimental group was mainly distributed in 0-2 grades, and the control group was mainly distributed in 1-3 grades, and the distribution of grades was statistically significant ($P < .01$). In terms of the average grade of chronic OIPN neurotoxicity, the average grade of the experimental group was 1, and the average grade of the control group was 2. The experimental group had a lower average grade of peripheral neurotoxicity after treatment ($P < .01$). See Table 6.

Table 6. Classification of peripheral nerve toxicity before and after treatment

Time	Group	Number of cases	WHO classification of peripheral neurotoxicity of antineoplastic drugs					Average grade (M)
			0	1	2	3	4	
Before treatment	Experimental Group	31	0	0	24	7	0	2
	Control Group	29	0	0	16	13	0	2
After treatment	Experimental Group	31	6	18	6	1	0	1[a]
	Control Group	29	0	7	17	5	0	2

[a]Compared with the control group after treatment, $P < .01$.

Total Neuropathy score (TNSc)

For intra-group comparison, there was a significant difference in the TNSc score between the two groups after treatment and before treatment ($P < .01$). There was no significant difference in the TNSc score between the two groups before treatment ($P > .05$). After treatment, the TNSc score in the experimental group was lower than that in the control group ($P < .01$), and the difference in the TNSc score before and after treatment in the experimental group was higher than that in the control group ($P < .01$). See Table 7.

Table 7. Total neuropathy score before and after treatment (M (P_{25}, P_{75}))

Group	Number of cases	Before treatment	After treatment	Difference
Experimental Group	31	5 (3,6)	2 (1,2)[a,c]	3 (1,4)[b]
Control Group	29	5 (4,7.5)	4 (2,6)[a]	1 (0,2)

[a]Compared with this group before treatment, $P < .01$
[b]Compared with control group, $P < .01$
[c]Compared with the control group after treatment, $P < .01$

Table 8. Chronic OIPN symptom range score before and after treatment (M (P_{25}, P_{75}))

Group	Number of cases	Before treatment	After treatment	Difference
Experimental Group	31	5 (3,7.5)	1.5 (0.5, 3)[a,c]	3 (1.5,5)[b]
Control Group	29	5 (3,7)	3 (1.75,5)[a]	1.5 (0,2)

[a]Compared with this group before treatment, $P < .01$
[b]Compared with control group, $P < .01$
[c]Compared with the control group after treatment, $P < .01$

Table 9. Comparison of KPS scores before and after treatment (M (P_{25}, P_{75}))

Group	Number of cases	Before treatment	After treatment	Difference
Experimental Group	31	90 (80,90)	90 (80,90)[a]	0 (0,0)
Control Group	29	90 (80,90)	90 (80,90)[a]	0 (0,0)

[a]Compared with this group before treatment, $P < .01$

Chronic OIPN symptom range score

For intra-group comparison, the symptom range scores of the two groups after treatment were significantly different from those before treatment ($P < .01$). There was no significant difference in chronic OIPN symptom range score between the two groups before treatment ($P > .05$). After treatment, the symptom range score of the experimental group was lower than that of the control group ($P < .01$), and the difference in symptom range score of the experimental group was higher than that of the control group ($P < .01$). See Table 8.

KPS score

Intra-group comparison: the KPS scores of the two groups after treatment were significantly different from those before treatment ($P < .01$). There was no significant difference in the KPS scores between the two groups before treatment and after treatment ($P > .05$). See Table 9.

Adverse events

Mecobalamine has gastrointestinal adverse reactions, such as loss of appetite, nausea, vomiting, diarrhea, etc. Allergic reactions such as rash and urticaria are rare. The centipede in Quma Tongluo recipe may have allergic reactions such as skin erythema, itching and papules.Among the patients who finally completed the trial, 29 patients in the control group had no adverse events, and 1 patient in the experimental group of 31 had diarrhea, which improved after symptomatic treatment (oral berberine hydrochloride tablets). The incidence of adverse drug reactions of Quma Tongluo prescription was about 3.2%, and the incidence of adverse drug reactions of mecobalamine was 0%.

DISCUSSION

Chronic OIPN is mainly manifested as numbness or pain in hands and feet that is difficult to heal for a long time after drug withdrawal, which is aggravated by cold, which limits the clinical application of oxaliplatin to a certain extent and seriously affects the quality of life of patients. OIPN is a potential permanent side effect of colorectal cancer treatment, so it is very necessary to study the pathogenesis of OIPN and strengthen the prevention and treatment of OIPN.The pathogenesis of acute and chronic OIPN is different,[22] At present, the pathogenesis of chronic OIPN is not completely clear. Existing studies suggest that chronic OIPN is mainly related to sodium channel dysfunction,[23] neuronal nuclear DNA damage,[24] neuronal mitochondrial damage,[25] down-regulation of nerve growth factor,[26] neuroinflammation,[27] etc.

Although many mechanisms and clinical trials have been conducted, the pathogenesis of chronic OIPN is not completely clear so no mature prevention and treatment system has been established. OIPN has very limited treatments for pain symptoms, the ASCO guideline only recommends duloxetine for CIPN-related neuropathic pain, and the efficacy is not good for chronic numbness syndrome. Some drugs such as Venlafaxine, pregabalin, and carbamazepine have also been evaluated, but their effectiveness in preventing oxaliplatin induced CIPN remains controversial. At present, clinical empirical selection of neurotrophic agents, antioxidants, cytoprotectants, neurotransmitter reuptake inhibitors, calcium and magnesium mixture, such as mecobalamin, adenosine cobalamin, and reduced glutathione.[28]

Traditional plant-based medicines (TMs) have been widely used to prevent chronic oxaliplatin-induced peripheral neurotoxicity (OIPN). Studies have shown that oral Chinese medicine seems to significantly reduce the incidence of chronic disease.TMs appear to be effective and safe in the prevention of chronic OIPN,especially severe chronic OIPN.[21]Traditional Chinese medicine has the characteristics of multi-component and multi-target treatment, which has great research value in the treatment of OIPN.

Although there is no related record of OIPN in ancient Chinese medical books, it can be classified into the categories of "blood-arthralgia", "Bi syndrome", "insensitivity", and "Collateral disease" according to the typical clinical manifestations of numbness and pain in the hands and feet, aggravation in the cold, and acral sensory disturbance. Most modern physicians think OIPN is mainly due to normal operation of qi and blood not reaching the tissue space of the muscle. The syndrome types are mainly qi and blood deficiency syndrome, Yang deficiency and cold coagulation syndrome, and blood stasis and internal obstruction syndrome. At present, the relevant research focuses on the prevention and treatment of acute OIPN, but the relevant research on chronic OIPN is less.

Synopsis of Golden Chamber discusses that the description of "pathogenic factors lies in collateral then the skin is not numb" of wind is highly similar to the clinical

characteristics of chronic OIPN with insensitivity as the main symptom, so chronic OIPN can be classified as "collars disease". In "Suwen·Discussion on Pain", "When the cold guest is outside the pulse, the pulse is cold; when the pulse is cold, the pulse is curled up; when the pulse is curled up, the pulse is deficient, and the deficiency is urgent, so the pain is sudden", which is very similar to the electrocut-like quenching pain of chronic OIPN when it is stimulated by cold. "Discussion on Wind" said: "The wind hurts the human body, and the Wei Qi has congealed and not done, so the skin and muscles feel numb" points out that the wind evil invades the meridians of the human body, and fights against Wei Qi in the muscles, so that the vein is blocked, and Wei Qi can not operate normally, and can not warm the skin and flesh and appear numb. Ling Xiaowu, a doctor in the Qing Dynasty, stated that the main symptom of wind disease was "finger numbness", which corresponded with the "glove and stocking pattern" of chronic OIPN numbness. Therefore, it is believed that oxaliplatin drug toxicity is wind-cold attribute, wind-cold withdrawal, acute choroidal clonicity, non-continuation of Qi-blood yin-yang, poor circulation of Qi-blood in the extremities, and insufficient of the Qi-blood in the hands and feet, resulting in numbness, cold pain and other symptoms, and pathological products such as chronic blood stasis further block choroidal veins, leading to deficiency of choroidal veins and difficult recovery, and the course of the disease is prolonged and difficult to cure. Professor Hou Fenggang proposed that the basic pathogenesis of chronic OIPN is wind-moving collaterals, asthenia, and cold stasis to cure the wind to relieve spasms, activating blood circulation, lifting the extremities of the vein spasm, activating blood circulation and remove blood stasis, restoring the extremities of the vein ying Wei Qi and blood flow smoothly, then the qi and blood flow around, the muscles are raised, and the symptom can be eliminated.

Quma Tongluo prescription is a protocol prescription in Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine. It was formulated according to the pathogenesis of chronic OIPN "wind-moving collateralization, asthenia combined with cold stasis". It was composed of Caulis spatholobi 30 g, large-leaved gentian 18 g, silkworm excrement 18 g, centipede 3 g. The pathogenesis of chronic OIPN in traditional Chinese Medicine is summarized as follows: unpatency of meridians and insufficient nutrition. Caulis spatholobi is the main drug in the prescription, which has the effect of nourishing blood and promoting blood and dispelling wind, referring to the idea of "treating the wind first, and eliminating the blood from the wind itself.", it can reduce the adverse effects of the wind evil by replenishing the blood, and then reduce the clonus of the nerves. Large-leaved gentian and silkworm excrement are mostly used for wind-dampness arthralgia, which has the effect of dispelling wind-dampness, relaxing muscles and blocking arthralgia pain. The effect of centipede is to soothe wind and stop spasmodic, relieve pain, promote blood circulation and remove blood stasis, detoxify and dissipate knots. The description of the centipede in Medicine is "the fastest walking main body, inside the viscera, outside the meridians, where the qi and blood coagulation can be opened", so the centipede can assist other pharmaceutical ingredients in reaching the end of the hands and feet. The whole prescription can dispel wind, relieve spasms, nourish blood, and channel collaterals.

The TCM contained in Quma Tongluo Formula also showed the research value in the treatment of peripheral neuropathy in terms of pharmacology. Modern Chinese medicine pharmacology studies have found that flavonoids contained in Caulis spatholobi can effectively inhibit platelet aggregation and thrombosis, so as to play the role of blood circulation and blood stasis, and relevant studies have confirmed that total flavonoids of Caulis spatholobi can reduce the mechanical pain sensitivity of neuropathic pain rats. Clinical studies have found that high-dose Cauli spatholobi has a good therapeutic effect in the treatment of neuropathy, and can significantly increase the level of nerve growth factor (NGF) in plasma of patients with neuropathy. Studies have shown that large-leaved gentian has a significant effect on the cholinergic pathway in the KEGG pathway and also on the dopaminergic neural pathway. Through multiple targets, large-leaved gentian can regulate the interaction between inflammatory factors and neural pathways, affect the diameter of blood vessels, and thus play a role in reducing neuropathic pain.The main active components of silkworm excrement are amino acids, flavonoids, alkaloids and trace elements, which can reduce inflammation and promote hematopoietic function. Centipede contains fatty acids, peptides, sugars, proteins, amino acids, cholesterols and trace elements and other chemical components, with obvious analgesic sedation, anti-inflammatory antispasmolytic effect, can improve microcirculation, prolong coagulation time, reduce blood viscosity, and thus play an anticoagulation, anti-platelet aggregation effect, among which anti-inflammatory analgesic effect is mostly used in the treatment of neuroinflammatory diseases.

In this study, patients with acute OIPN and chronic OIPN with a certain tendency of self-healing were excluded, and patients with chronic OIPN who had finished oxaliplatin chemotherapy and showed no relief of symptoms for more than 1 week were selected as the study objects. In clinical practice, most of these patients chose to coexist with OIPN due to a lack of effective treatment, which had a great impact on the quality of life. Therefore, the active intervention of traditional Chinese Medicine is very important. The results of this study showed that Quma Tongluo prescription can effectively treat oxaliplatin-related chronic peripheral neuropathy and reduce the quantified score of chronic peripheral neuropathy severity, numbness quantified score, CIPN 20 score, TNSc score, peripheral neurotoxicity grade, and chronic OIPN symptom range score. The effective rate was high (87.1%). However, both Quma Tongluo prescription and mecobalamine tablet can improve pain quantification score and KPS score to a certain extent, but there is no significant difference in efficacy between them. The analysis shows that when OIPN extends to

the chronic stage, the clinical manifestations of patients are mainly insensitive, and the degree and frequency of cold tenderness are lower than those in the acute stage. Moreover, the study found that the overall KPS score of patients with chronic OIPN was high, ranging from 80 to 90 points, indicating that chronic OIPN had little impact on the overall physical strength score of patients.

The results of this study showed that Quma Tongluo prescription could significantly reduce the degree of numbness of chronic OIPN, narrow the range of symptoms, and reduce the neurotoxicity grade and related neuropathy score of chronic OIPN. The total effective rate and significant efficiency were higher than mecobalamine, no obvious adverse reactions were observed, and the safety was good, which had certain clinical and research value. It was concluded that the oxaliplatin induced chronic nerve injury may be caused by multiple mechanisms of action, and a single neuronutrient cannot effectively repair it. However, TCM compounds contain more effective components, which may play a role in nerve injury of chronic OIPN through multi-pathway and multi-target.

Since there is still no effective prevention and treatment plan for chronic OIPN recommended by the guidelines, permanent and irreversible nerve damage that may be caused by oxaliplatin has to be considered in clinical chemotherapy, which will reduce patients' compliance with chemotherapy and force them to suspend or terminate chemotherapy. Based on the theory of traditional Chinese medicine, this study focuses on exploring the effective treatment of chronic OIPN. Studies have shown that Quma Tongluo formula can significantly improve the clinical symptoms of patients with chronic OIPN, improve the quality of life of patients by reducing the numbness, tingling and hand-foot weakness of patients, and reduce the risk of patients with sensory and motor nerve injury caused by instability, scalding, falling and other injuries. Effective chronic OIPN treatment program can solve the side effects of chemotherapy for tumor patients to a certain extent, which may affect clinical decision-making, reduce patients' resistance to chemotherapy, help patients complete the whole course of chemotherapy, and provide effective treatment measures for patients with subsequent chronic irreversible nerve damage.

However, there are still many limitations in this study. This study lacks some objective measurement indicators. Due to relevant factors in the actual study (such as low patient compliance), objective safety measures (such as liver and kidney function, blood routine), and objective efficacy measures (such as EMG) were not fully collected. We plan to add therapeutic indicators such as electromyography and nerve growth factor in subsequent studies, and improve the measurement of safety indicators such as blood routine and liver and kidney function to further increase the reliability of the study results.

Due to the small sample size, the conclusions drawn in this study have certain limitations.Adverse drug reactions were also observed in only 1 patient with diarrhea, and the relationship between diarrhea and therapeutic drugs could not be clarified due to the small sample size.In the later study, multi-center and large sample clinical trials can be further carried out to observe its efficacy and adverse reactions. The optimal intervention time of this formula still needs to be further explored. The specific pharmacological mechanism of this prescription for chronic OIPN is still unclear and needs to be confirmed by further pharmacological experiments.

In this study, the traditional Chinese medicine prescription under the guidance of traditional Chinese medicine theory is used to treat chronic OIPN, which has the advantages of multi-component and multi-target of traditional Chinese medicine compound, but also has difficulties in follow-up exploration of pharmacological mechanism due to the complexity of active ingredients. There is still much room for research on the use of traditional Chinese medicine in the treatment of cancer and related side effects, and many challenges need to be faced, such as: Whether there is an accurate intervention time for TCM compounds to treat chronic OIPN, whether there is an optimal ratio and dosage for each Chinese medicine, whether the compound affects the efficacy of chemotherapy drugs, whether the individual treatment of TCM can be expanded to group treatment, how to quantify the efficacy of TCM, and so on.

According to current research, the course of chronic oxaliplatin associated peripheral neuropathy is still not clearly defined. Based on the characteristics that acute symptoms can generally be relieved within 1 week, this study initially defined the course of chronic oxaliplatin induced peripheral neuropathy. We defined chronic OIPN as chronic OIPN for those who did not see symptom relief after 1 week of drug suspension, and took this as the inclusion criteria for chronic OIPN. However, this criterion is relatively vague, and subsequent studies may limit the course of chronic OIPN by the median recovery time of 12-13 weeks. Nevertheless, the course diagnosis of chronic OIPN remains to be further studied and clarified, which may be closely related to the mechanism study of chronic OIPN. For example, in the future, acute and chronic OIPN may be diagnosed separately from the perspective of pathological features.

ETHICAL COMPLIANCE

The ethics committee of Shanghai Municipal Hospital of Traditional Chinese Medicine approved this study. Signed written informed consents were obtained from the patients and/or guardians.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

JJ: Conceptualization, methodology, writing original draft preparation. CS, YY: Investigation, software. MD, YT and XY: Investigation, statistical analysis. FH: Reviewing and editing, funding acquisition, supervision. All authors read and approved the final manuscript.

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