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Article

A Retrospective Comparative Study of Sodium Ferulate Combined With Methylcobalamin for Oxaliplatin-Induced Peripheral Neuropathy in Patients With Colorectal Cancer

Baojun Min[1], Li Wan[2], Hongyong He[1], Jie Chen[1], Zhonglu Jian[3,*], Rong Chen[3,*]

[1]Department of Anesthesiology, Qianxi People's Hospital, 551599 Bijie, Guizhou, China
[2]Department of Pain, Qianxi People's Hospital, 551599 Bijie, Guizhou, China
[3]Department of Anesthesiology, The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, 550001 Guiyang, Guizhou, China
*Correspondence: 18984385335@139.com (Zhonglu Jian); binqijialin@126.com (Rong Chen)
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Abstract

Aims/Background: Oxaliplatin-induced peripheral neuropathy (OIPN) is a common dose-limiting toxic effect of oxaliplatin-based chemotherapy for colorectal cancer (CRC), severely affecting patients' quality of life and treatment adherence. Currently, effective therapeutic options for OIPN are limited. This study aimed to investigate the clinical efficacy and safety of sodium ferulate combined with methylcobalamin in the treatment of OIPN in CRC patients. **Methods**: In this retrospective cohort study, 280 CRC patients diagnosed with OIPN following oxaliplatin-based chemotherapy at Qianxi People's Hospital between January 2020 and December 2024 were enrolled. Based on treatment regimen, patients were assigned to an observation group (sodium ferulate combined with methylcobalamin, $n = 152$) or a control group (methylcobalamin alone, $n = 128$). All patients received basic nursing care. Treatment duration was 8 weeks for both groups. Outcomes compared between groups included National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) neurotoxicity grading, nerve conduction velocity (NCV), and quality of life (QoL) scores assessed before treatment, at 4 weeks, and at 8 weeks post-treatment. Clinical efficacy was evaluated after 8 weeks, and changes in hematological parameters and liver/kidney function indicators were monitored. **Results**: Baseline characteristics were comparable between the two groups ($p > 0.05$). While no significant difference in neurotoxicity grading was observed at 4 weeks ($p > 0.05$), the observation group demonstrated significantly better NCI-CTCAE grades than the control group at 8 weeks ($p < 0.05$). NCV assessments revealed that motor and sensory NCVs of the median and common peroneal nerves in the observation group were significantly improved compared to both baseline levels and the control group at 4 and 8 weeks ($p < 0.05$). After 8 weeks, the overall clinical efficacy rate was significantly higher in the observation group (89.47%) than in the control group (67.97%) ($p < 0.05$). QoL scores across all functional domains (physical, role, cognitive, emotional, and social) were significantly better in the observation group compared to the control group at 8 weeks ($p < 0.05$). Hematological and liver/kidney function parameters remained within normal ranges and showed no significant intergroup differences post-treatment ($p > 0.05$). **Conclusion**: The combination of sodium ferulate and methylcobalamin is superior to methylcobalamin monotherapy in alleviating the severity of neurotoxicity, improving nerve conduction function, enhancing clinical efficacy, and promoting quality of life in CRC patients with OIPN, with a comparable safety profile. It represents a promising clinical treatment option for OIPN.

Keywords: colorectal cancer; oxaliplatin; peripheral neuropathy; sodium ferulate; methylcobalamin

1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer-related death worldwide, posing a major public health challenge [1,2,3]. According to GLOBOCAN 2020 data published by the World Health Organization's International Agency for Research on Cancer (IARC), there are over 1.9 million new cases of CRC and approximately 930,000 deaths each year, with incidence and mortality continuing to rise, particularly in countries undergoing social and economic transition [4]. In China, driven by westernization of lifestyle and diet and an aging population, the burden of CRC has intensified [5]. It has become the second most common malignant tumor of the digestive tract and poses a serious threat to public health [6].

Oxaliplatin-based chemotherapy regimens (e.g., FOLFOX [folinic acid, fluorouracil, oxaliplatin] and XELOX [capecitabine, oxaliplatin]) are important options for adjuvant and advanced treatment of CRC [7,8]. Oxaliplatin exerts its cytotoxic effect by forming platinum–DNA adducts that inhibit DNA replication and transcription, inducing tumor cell apoptosis and significantly improving patient survival [9,10]. However, its dose-limiting toxicity—oxaliplatin-induced peripheral neuropathy (OIPN)—severely restricts the clinical use of oxaliplatin-based chemotherapy and is a major challenge in patient management [11]. OIPN predominantly presents as sensory nerve dysfunction, with common symptoms including distal limb sensory disturbances, numbness and pain [12]. Its toxicity is clearly dose-dependent, worsening pro-

gressively with each treatment cycle, markedly reducing patients' quality of life and potentially resulting in long-term functional impairment [13,14]. More importantly, to avoid irreversible nerve damage, clinicians often reduce oxaliplatin dose, delay, or discontinue treatment—actions that can compromise antitumor efficacy and long-term survival [15]. Therefore, the development of effective strategies for the prevention and treatment of OIPN represents a key unmet need in CRC care.

At present, clinical management of OIPN remains highly challenging due to limited effective therapeutic options. Notably, the 2020 American Society of Clinical Oncology (ASCO) guideline update identified duloxetine as the only agent for the treatment of established OIPN [16]. In practice, symptomatic and supportive measures are commonly used, including pharmacologic interventions (e.g., tricyclic antidepressants, anticonvulsants, analgesics), nonpharmacologic approaches (e.g., temperature management, exercise, complementary therapies), and chemotherapy regimen modification—the latter being the most frequently used clinical approach [17,18]. These measures have clear limitations: although duloxetine shows some benefit, its use is limited by adverse effects such as nausea, somnolence, and dry mouth, and overall response rates are suboptimal [19,20]. The calcium-magnesium infusion that has been utilized for OIPN prevention remains controversial because of potential impacts on tumor outcomes [21]. This paucity of effective, reliably proven treatments highlights the urgent need to explore novel, effective interventions.

Against this background, drug combinations that offer both neuroprotection and neurorepair have attracted attention. Methylcobalamin, an active coenzyme form of vitamin B12, readily enters neural cells, promotes nucleic acid, protein, and myelin synthesis, and accelerates peripheral nerve repair and regeneration [22,23]. Sodium ferulate is the sodium salt form of ferulic acid, which has multiple pharmacological effects such as antioxidant, anti-inflammatory, microcirculation improvement, and neural nutrition [24]. Based on the pathogenesis of OIPN and the pharmacological profiles of sodium ferulate and methylcobalamin, we hypothesize that combining sodium ferulate with methylcobalamin may enhance treatment outcomes for OIPN: sodium ferulate mitigates oxidative stress and microcirculatory disturbances to create a favorable milieu for nerve repair, while methylcobalamin promotes regeneration of injured nerve fibers; together, they may synergistically improve nerve function. To test this hypothesis, we conducted a retrospective analysis comparing the efficacy and safety of sodium ferulate combined with methylcobalamin versus methylcobalamin alone for treating OIPN in patients with CRC, with the aim of providing a superior clinical treatment option.

2. Methods

2.1 Study Population

This retrospective cohort study reviewed the medical records of patients with CRC who developed OIPN after receiving oxaliplatin-based chemotherapy in the Departments of Oncology and Gastroenterology at Qianxi People's Hospital between January 2020 and December 2024. Patients were assigned to the two treatment groups according to the clinical decisions made by attending physicians during the standard care process, and all neurotoxicity assessments (including National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading and nerve conduction velocity measurements) were subsequently performed by pain specialists. Specifically, the selection of combination therapy (sodium ferulate and methylcobalamin) versus monotherapy (methylcobalamin alone) was primarily guided by factors such as the severity of neuropathic symptoms at presentation, the treating physician's clinical judgment and experience with the regimens, and the patient's overall clinical condition and potential contraindications. A total of 350 patients were initially identified. After applying the predefined inclusion and exclusion criteria, 280 eligible patients were enrolled in the final analysis. Among them, 152 patients who received sodium ferulate combined with methylcobalamin were assigned to the observation group, whereas 128 patients who received methylcobalamin monotherapy were assigned to the control group. The study was approved by the medical Ethics Committee of Qianxi People's Hospital (Approval Number: 20220803). Fig. 1 presents a flow diagram illustrating the steps of subject screening, exclusion, and final group assignment.

2.2 Inclusion Criteria and Exclusion Criteria

Inclusion criteria of this study are as follows: (1) age $\geq$18 years; (2) histological or cytological confirmation of CRC; (3) development of peripheral neuropathic symptoms following oxaliplatin-based chemotherapy. The diagnosis of OIPN was based on typical chemotherapy-induced peripheral neuropathy (CIPN) manifestations, including symmetrical distal numbness, tingling, hypoesthesia, and neuropathic pain [16]. Neurotoxicity severity was graded using the NCI-CTCAE (version 5.0) peripheral sensory neuropathy criteria, and patients with grades 1–4 were included [25]; (4) availability of complete clinical data; and (5) no exposure to other chemotherapy regimens within 3 months before enrollment.

Exclusion criteria of this study are as follows: (1) peripheral neuropathy attributable to other causes; (2) impaired liver function, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>2.5\times$ the upper limit of normal, or impaired renal function, defined as serum creatinine (Scr) $>1.5\times$ the upper limit of normal; (3) allergy to sodium ferulate, methylcobalamin, or oxaliplatin; (4) presence of concomitant severe infection, cardiovascular or cerebrovascular disease, or another malignancy; (5)

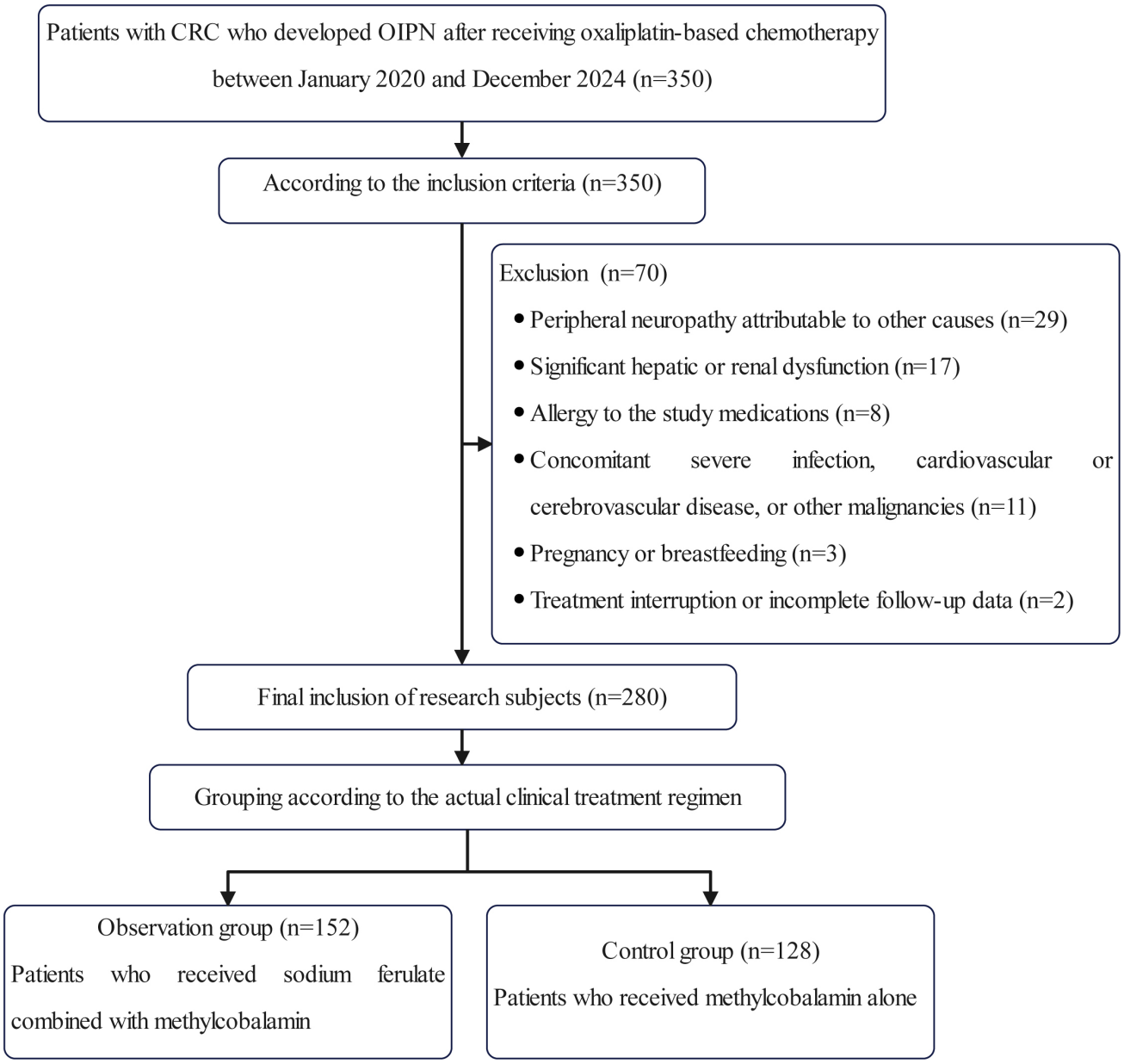

Fig. 1. Flow diagram depicting patient selection and grouping process. The figure was created using EdrawMax software (Version 14.0.0, Wondershare Technology Co., Ltd., Changsha, China). Abbreviations: CRC, colorectal cancer; OIPN, oxaliplatin-induced peripheral neuropathy.

treatment interruption during the study period or incomplete follow-up data; and (6) pregnancy or breastfeeding.

2.3 Treatment Regimen

All patients received basic nursing care and continued to receive their oxaliplatin-based chemotherapy regimen during the 8-week study intervention period. The dose and cycles of oxaliplatin were adjusted as necessary by the treating physicians based on clinical assessment of neurotoxicity and standard oncology care. Patients in the control group received methylcobalamin monotherapy (CSPC Ouyi Pharmaceutical Co., Ltd., Shijiazhuang, China; Catalog No.: H20050168) at a dose of 0.5 mg, administered once daily via intravenous injection. In addition to the aforementioned treatment, subjects in the observation group were supplemented with sodium ferulate (Jiangsu Shenlong Pharmaceutical Co., Ltd., Yancheng, China; Catalog No.: H32026219) at a dose of 300 mg, administered once daily via intravenous infusion. Each course of treatment consisted of consecutive administration for 4 weeks, with a total of 2 courses completed. The overall treatment duration was 8 weeks.

2.4 Baseline Data Collection

Baseline patient data were extracted through the hospital's electronic medical record (EMR) system and laboratory information system (LIS). Demographic and general clinical information included age, gender, body mass index

Table 1. Baseline characteristics between the control and observation groups.

Characteristic	Control group (n = 128)	Observation group (n = 152)	$t/\chi^2/Z$	p
Age (years), mean ± SD	56.46 ± 8.74	57.15 ± 7.65	–0.70	0.484
BMI (kg/m^2), mean ± SD	23.68 ± 2.04	23.37 ± 2.56	1.12	0.264
Chemotherapy cycles, M (Q1, Q3)	4.00 (4.00, 5.00)	4.00 (3.00, 4.00)	–1.60	0.109
Gender, *n* (%)			0.04	0.836
Male	70 (54.69)	85 (55.92)		
Female	58 (45.31)	67 (44.08)		
Tumor stage, *n* (%)			0.03	0.867
Stage III	100 (78.12)	120 (78.95)		
Stage IV	28 (21.88)	32 (21.05)		
Pathological type, *n* (%)			-	0.845
Mucinous adenocarcinoma	14 (10.94)	13 (8.55)		
Adenocarcinoma	110 (85.94)	134 (88.16)		
Signet ring cell carcinoma	4 (3.12)	5 (3.29)		
Primary tumor site, *n* (%)			0.14	0.713
Colon	73 (57.03)	90 (59.21)		
Rectum	55 (42.97)	62 (40.79)		
Surgical treatment, *n* (%)			0.26	0.878
Radical resection	77 (60.16)	95 (62.50)		
Palliative resection	23 (17.97)	24 (15.79)		
No surgery	28 (21.88)	33 (21.71)		
Chemotherapy regimen, *n* (%)			0.22	0.898
FOLFOX4	36 (28.12)	46 (30.26)		
FOLFOX6	58 (45.31)	65 (42.76)		
XELOX	34 (26.56)	41 (26.97)		
Previous chemotherapy history, *n* (%)	22 (17.19)	17 (11.18)	2.09	0.148
Smoking history, *n* (%)	18 (14.06)	20 (13.16)	0.05	0.826
Alcohol drinking history, *n* (%)	19 (14.84)	25 (16.45)	0.13	0.713
Hypertension, *n* (%)	36 (28.12)	33 (21.71)	1.54	0.215
Diabetes mellitus, *n* (%)	8 (6.25)	20 (13.16)	3.68	0.055
Hyperlipidemia, *n* (%)	18 (14.06)	31 (20.39)	1.93	0.165

Notes: Data are expressed as n (%), mean ± SD, or M (Q1, Q3). Categorical variables were analyzed using χ^2 test or Fisher's test. Continuous variables were analyzed using independent-samples *t*-test or Mann-Whitney *U* test. "-" indicates no specific statistical value. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) 8th edition [28].

Abbreviations: BMI, body mass index; FOLFOX, folinic acid, fluorouracil, oxaliplatin; XELOX, capecitabine, oxaliplatin; SD, standard deviation.

(BMI), smoking history, and alcohol consumption. Tumor-related data, such as pathological type, tumor stage, primary tumor site, history of surgical treatment, chemotherapy regimen, and chemotherapy cycles, were gathered. Information regarding comorbidities and medical history was collected, such as the presence of comorbidities (hypertension, diabetes, hyperlipidemia) and prior chemotherapy history. Results of laboratory tests, such as baseline complete blood count (white blood cell count, platelet count, hemoglobin), liver and renal function (ALT, AST, Scr, blood urea nitrogen [BUN]), were gleaned from the information system. Results of pre-treatment neurotoxicity grade and nerve conduction velocity (NCV), which constitute the neurological baseline assessment, were also obtained.

2.5 Assessed Parameters

2.5.1 Neurotoxicity Grade

The severity of OIPN in patients was assessed before treatment, and at 4 and 8 weeks after treatment initiation, with reference to the peripheral sensory neurotoxicity grading criteria specified in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) [25]. All NCI-CTCAE gradings were performed by two attending physicians from the Department of Anesthesiology who had received standardized training and had more than 5 years of clinical experience. In cases of disagreement, the two physicians discussed to reach a consensus; if no consensus could be achieved, a third senior attending physician from the same department was consulted to determine the final grade.

Table 2. NCI-CTCAE neurotoxicity grading between two patient groups before and after treatment (*n*, %).

Time points	NCI-CTCAE neurotoxicity grade	Control group (n = 128)	Observation group (n = 152)	χ^2	p
Before treatment	1	0 (0.00)	0 (0.00)	0.18	0.913
	2	65 (50.78)	74 (48.68)		
	3	49 (38.28)	62 (40.79)		
	4	14 (10.94)	16 (10.53)		
4 weeks after treatment	1	7 (5.47)	12 (7.89)	1.53	0.675
	2	67 (52.34)	85 (55.92)		
	3	48 (37.50)	50 (32.89)		
	4	6 (4.69)	5 (3.29)		
8 weeks after treatment	1	21 (16.41)	57 (37.50)	-	<0.001
	2	71 (55.47)	78 (51.32)		
	3	32 (25.00)	15 (9.87)		
	4	4 (3.12)	2 (1.32)		

Notes: Data are expressed as n (%). Categorical variables were analyzed using χ^2 test or Fisher's test. "-" indicates no specific statistical value.

Abbreviation: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 3. Nerve conduction velocity between the two groups before and after treatment [m/s, M (Q1, Q3)].

Time Points	Variables	Control group (n = 128)	Observation group (n = 152)	Z	p
Before treatment	Median nerve MNCV (m/s)	44.60 (42.50, 46.60)	45.60 (43.10, 47.10)	–1.35	0.176
	Median nerve SNCV (m/s)	41.10 (38.60, 42.50)	40.60 (38.20, 42.50)	–0.72	0.473
	Common peroneal nerve MNCV (m/s)	41.80 (39.80, 43.80)	41.30 (39.50, 42.80)	–1.27	0.203
	Common peroneal nerve SNCV (m/s)	36.20 (34.20, 37.60)	36.90 (35.20, 38.80)	–1.49	0.137
4 weeks after treatment	Median nerve MNCV (m/s)	47.30 (45.00, 49.30)**	49.80 (47.20, 52.00)**	–4.82	<0.001
	Median nerve SNCV (m/s)	42.40 (40.30, 44.20)*	43.80 (42.40, 45.90)*	–4.05	<0.001
	Common peroneal nerve MNCV (m/s)	44.20 (42.70, 45.80)*	45.70 (43.70, 47.90)**	–3.86	<0.001
	Common peroneal nerve SNCV (m/s)	37.90 (36.40, 39.30)*	40.70 (39.00, 42.70)**	–6.47	<0.001
8 weeks after treatment	Median nerve MNCV (m/s)	48.50 (45.90, 50.10)**	52.50 (50.50, 54.50)**	–7.67	<0.001
	Median nerve SNCV (m/s)	43.30 (41.70, 45.60)*	47.20 (44.40, 48.70)**	–6.39	<0.001
	Common peroneal nerve MNCV (m/s)	46.00 (44.60, 47.70)**	48.30 (46.50, 50.50)**	–5.42	<0.001
	Common peroneal nerve SNCV (m/s)	39.30 (37.80, 40.80)*	42.90 (40.90, 44.60)**	–8.01	<0.001

Notes: Data are expressed as M (Q1, Q3). Continuous variables were analyzed using Mann-Whitney U test for between-group comparisons. *$p < 0.05$, **$p < 0.01$ compared with before treatment within the same group.

Abbreviations: MNCV, motor nerve conduction velocity; SNCV, sensory nerve conduction velocity.

2.5.2 Nerve Conduction Velocity

The Keypoint® G4 electromyography (EMG) device (model G4; Natus Medical Incorporated, Middletown, New York, USA) was used to measure the motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) of the median nerve and common peroneal nerve in patients. All measurements were conducted under standardized testing conditions, including a room temperature of 25–28 °C and a skin temperature ≥32 °C, and were operated by the same experienced neurophysiologist.

2.5.3 Clinical Efficacy

Clinical efficacy was evaluated 8 weeks after the start of treatment. Based on patients' clinical symptoms and examination results, therapeutic response was classified into three categories: markedly effective, effective, and ineffective [26]. 'Markedly effective' was defined as near complete resolution of clinical symptoms (e.g., numbness and pain in the fingertips of the extremities, weakness in lower limbs during walking); restoration of deep and superficial sensations, as well as tendon reflexes, to near-normal levels; and an increase in MNCV and SNCV of ≥5 m/s compared with baseline (pre-treatment). 'Effective' was defined as alleviation of the aforementioned clinical symptoms; improvement in deep and superficial sensations, along with tendon reflexes, compared with baseline; and an increase in MNCV and SNCV of <5 m/s compared with baseline. 'Ineffective' was defined as no significant improvement in clinical symptoms, deep or superficial sensations, tendon reflexes, or electromyography (EMG) parameters compared with baseline. The overall clinical efficacy rate was computed using the following formula:

Overall clinical efficacy rate (%) = (Number of patients with markedly effective response + Number of patients with effective response) / Total number of patients × 100.

Table 4. Levels of clinical efficacy between the two groups after 8 weeks of treatment.

Variables		Control group (n = 128)	Observation group (n = 152)	χ^2	p
Clinical efficacy	Ineffective	41 (32.03)	16 (10.53)	21.69	<0.001
	Markedly effective	39 (30.47)	74 (48.68)		
	Effective	48 (37.50)	62 (40.79)		
Overall clinical efficacy rate		87 (67.97)	136 (89.47)	19.82	<0.001

Notes: Data are expressed as n (%). Categorical variables were analyzed using χ^2 test.

2.5.4 Quality of Life Assessment

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was used to assess the quality of life of patients before treatment, at 4 weeks, and at 8 weeks during the treatment period [27]. This scale includes five functional dimensions (physical function, role function, cognitive function, emotional function, and social function), all scored on a percentage scale, and the score is directly proportional to the quality of life.

2.5.5 Blood Routine and Liver and Kidney Function Indicators

Fasting venous blood (5 mL) was collected from patients before treatment, at 4 weeks, and at 8 weeks post-treatment. Blood routine indicators (white blood cell [WBC] count, platelet [PLT] count, hemoglobin [Hb]) were measured using an XN-9000 fully automatic blood cell analyzer (model XN-9000; Sysmex Corporation, Kobe, Hyogo, Japan), and liver and kidney function indicators (ALT, AST, Scr, BUN) were measured using a cobas® 8000 fully automatic biochemical analyzer (model cobas® 8000; Roche Diagnostics GmbH, Mannheim, Baden-Württemberg, Germany).

2.6 Statistical Analysis

Statistical analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Prior to formal analysis, the Shapiro-Wilk test was used to assess the normality of continuous variables. For continuous variables that conformed to a normal distribution, data are presented as mean $\pm$ standard deviation (SD), and between-group comparisons were conducted using independent-samples t-test. For continuous variables that did not follow a normal distribution, data are expressed as median (interquartile range) [M (Q1, Q3)], with between-group comparisons performed using the Mann-Whitney U test and within-group comparisons using the Wilcoxon signed-rank test. Categorical variables are presented as numbers (percentages) [n (%)], and comparisons between groups were carried out using the χ^2 test; Fisher's exact test was adopted when the expected frequency of any cell was <5. Rank sum test was used for comparing grade data. A $p < 0.05$ was considered statistically significant.

3. Results

3.1 Baseline Characteristics of the Two Patient Groups

A total of 280 CRC patients with OIPN were enrolled in this study, with 152 patients in the observation group and 128 in the control group (Table 1, Ref. [28]). No statistically significant differences were observed between the two groups in terms of demographic characteristics, disease-related characteristics, lifestyle habits, or comorbidities at baseline ($p > 0.05$ for all comparisons), indicating that the baseline characteristics of the two groups were generally comparable.

3.2 NCI-CTC Neurotoxicity Grade of the Two Patient Groups

A comparison of NCI-CTCAE neurotoxicity grades between the two patient groups before and after treatment is shown in Table 2. At baseline, the distribution of neurotoxicity grades was comparable between the two groups ($p > 0.05$). At 4 weeks after treatment, the difference in grade distribution between the two groups was not statistically significant ($p > 0.05$). However, by 8 weeks after treatment, the intergroup difference in neurotoxicity grade distribution became statistically significant ($p < 0.05$), with the observation group showing a notably more favorable grade distribution compared to the control group.

3.3 Nerve Conduction Velocity of the Two Groups

As detailed in Table 3, the MNCV and SNCV of the median and common peroneal nerves were comparable between the two groups before treatment ($p > 0.05$). After treatment, both groups showed significant improvement in all NCVs compared to their respective baseline levels ($p < 0.05$). Importantly, at both 4 and 8 weeks after treatment, all NCV parameters in the observation group were significantly higher than those in the control group ($p < 0.05$ for all comparisons).

3.4 Clinical Efficacy of the Two Groups

As shown in Table 4, after 8 weeks of treatment, the overall clinical efficacy rate in the observation group was significantly higher than that in the control group (89.47% vs. 67.97%, $p < 0.05$). The distribution of patients across the specific clinical efficacy categories also differed significantly between the groups.

Table 5. Quality-of-life assessment between the two groups at baseline, 4 weeks, and 8 weeks after treatment.

Time points	Variables	Control group (n = 128)	Observation group (n = 152)	Z	p
Before treatment	Physical functioning	53.10 (49.40, 57.60)	52.20 (48.10, 55.80)	–0.83	0.404
	Role functioning	47.60 (43.90, 53.00)	48.90 (44.90, 53.40)	–0.86	0.387
	Cognitive functioning	55.00 (50.10, 60.70)	55.70 (51.60, 59.70)	–0.29	0.769
	Emotional functioning	48.90 (44.90, 52.70)	50.10 (46.20, 54.40)	–1.53	0.127
	Social functioning	49.30 (42.50, 54.30)	48.50 (44.00, 54.10)	–0.05	0.961
4 weeks after treatment	Physical functioning	60.20 (55.80, 64.10)*	68.90 (64.20, 72.50)**	–7.92	<0.001
	Role functioning	55.80 (51.50, 59.60)*	65.30 (61.20, 69.50)**	–8.45	<0.001
	Cognitive functioning	58.90 (54.20, 63.50)	70.10 (65.80, 74.20)**	–9.13	<0.001
	Emotional functioning	56.40 (52.10, 60.80)*	67.20 (63.00, 71.50)**	–8.76	<0.001
	Social functioning	54.70 (49.80, 59.20)*	65.50 (61.10, 69.80)**	–8.21	<0.001
8 weeks after treatment	Physical functioning	67.60 (62.80, 70.40)**	79.90 (74.00, 83.70)**	–9.45	<0.001
	Role functioning	62.30 (58.50, 66.50)**	74.80 (70.50, 79.80)**	–9.69	<0.001
	Cognitive functioning	66.50 (60.80, 70.80)**	80.30 (75.30, 83.80)**	–10.00	<0.001
	Emotional functioning	64.20 (59.50, 68.30)**	77.00 (71.80, 81.60)**	–9.65	<0.001
	Social functioning	61.10 (56.10, 66.70)**	73.80 (69.20, 78.50)**	–9.30	<0.001

Notes: Data are expressed as M (Q1, Q3). Between-group comparisons of continuous variables were analyzed using Mann-Whitney U test. *$p < 0.05$, **$p < 0.01$ compared with before treatment within the same group.

3.5 Quality of Life Assessment of the Two Groups

The quality-of-life assessment results are summarized in Table 5. At baseline, no significant differences were observed between the two groups across all functional domains ($p > 0.05$). At the 4-week assessment, the observation group demonstrated statistically significant improvements in quality-of-life scores compared to the control group across all functional domains (all $p < 0.05$). After 8 weeks of treatment, the between-group differences further increased, with the observation group maintaining significantly superior scores compared to the control group in all functional domains (all $p < 0.05$).

3.6 Complete Blood Count and Liver and Kidney Function of the Two Groups

The hematological and liver/kidney function parameters for both groups are summarized in Table 6. At baseline, there were no statistically significant differences in any of the measured indicators between the control and observation groups ($p > 0.05$). Within-group comparisons showed that none of the parameters exhibited statistically significant changes from baseline at either the 4-week or 8-week time points ($p > 0.05$). Between-group comparisons revealed no statistically significant differences in any of these indicators at 4 or 8 weeks after treatment ($p > 0.05$), indicating a comparable safety profile of the combination therapy versus the monotherapy.

4. Discussion

This study retrospectively analyzed the efficacy and safety of sodium ferulate combined with methylcobalamin versus methylcobalamin monotherapy in the treatment of OIPN in CRC patients. The results demonstrated that the combination therapy exhibited significant superiority over the monotherapy in terms of neurotoxicity grading, NCV, overall clinical efficacy, and multiple dimensions of quality of life, with comparable safety and no increased risk of adverse reactions.

Although most baseline characteristics were well balanced, the prevalence of diabetes mellitus was higher in the observation group than in the control group (13.16% vs. 6.25%), with a p-value approaching statistical significance ($p = 0.055$). This near significant difference may reflect clinician preference for combination therapy in patients with diabetes—a known risk factor for neuropathy—or be due to the non randomized, retrospective design. The study found that patients in the observation group demonstrated improvements in NCI-CTCAE neurotoxicity grades at both 4 and 8 weeks post-treatment, with the difference between groups reaching statistical significance at 8 weeks post-treatment. Specifically, the proportion of patients with Grade 1 neurotoxicity in the observation group was notably higher than that in the control group (37.50% vs. 16.41%), while the proportion of Grades 3–4 neurotoxicity was significantly lower (11.19% vs. 28.12%). These findings indicate that the combination of sodium ferulate with methylcobalamin can substantially mitigate the severity of neurotoxicity, with effects becoming more pronounced over time. This synergistic action stems from the complementary multi-target mechanisms of the two drugs: mecobalamin, as an active form of vitamin B12, promotes myelin synthesis and axonal regeneration [29]; while sodium ferulate exerts antioxidant, anti-inflammatory, and microcirculation-improving effects [30]. Together, these beneficial effects address the core pathological processes of OIPN. The development and progression of OIPN are primarily associated with oxidative stress, mitochondrial dysfunction, and subsequent neuroinflammation, ultimately leading to neuronal damage and im-

Table 6. Complete blood count and liver and kidney function between the two groups at baseline, 4 weeks, and 8 weeks after treatment.

Time points	Variables	Control group (n = 128)	Observation group (n = 152)	Z	p
Before treatment	WBC ($\times 10^9$/L)	5.89 (4.96, 6.82)	5.85 (5.00, 6.78)	–0.42	0.676
	PLT ($\times 10^9$/L)	239.00 (198.00, 263.00)	229.00 (192.00, 263.00)	–0.88	0.380
	Hb (g/L)	128.90 (117.10, 137.90)	128.80 (119.60, 139.30)	–0.50	0.616
	ALT (U/L)	23.40 (19.40, 27.60)	23.10 (20.10, 27.20)	–0.09	0.929
	AST (U/L)	21.80 (18.40, 24.30)	22.80 (18.70, 26.00)	–1.13	0.259
	Scr (µmol/L)	68.50 (61.50, 72.80)	68.70 (59.80, 73.90)	–0.41	0.685
	BUN (mmol/L)	5.21 (4.45, 5.76)	5.36 (4.67, 6.25)	–1.67	0.095
4 weeks after treatment	WBC ($\times 10^9$/L)	5.89 (5.00, 6.60)^{ns}	5.67 (4.81, 6.34)^{ns}	–0.54	0.588
	PLT ($\times 10^9$/L)	237.00 (210.00, 263.00)^{ns}	229.00 (199.00, 266.00)^{ns}	–0.77	0.443
	Hb (g/L)	129.70 (119.80, 138.30)^{ns}	129.70 (122.90, 137.50)^{ns}	–0.04	0.966
	ALT (U/L)	23.30 (19.00, 27.50)^{ns}	23.20 (20.00, 26.90)^{ns}	–0.13	0.894
	AST (U/L)	21.10 (18.30, 24.00)^{ns}	21.20 (19.00, 24.70)^{ns}	–0.82	0.410
	Scr (µmol/L)	66.80 (59.00, 75.90)^{ns}	66.00 (59.80, 73.20)^{ns}	–0.51	0.613
	BUN (mmol/L)	5.16 (4.49, 5.54)^{ns}	5.35 (4.73, 5.78)^{ns}	–1.71	0.087
8 weeks after treatment	WBC ($\times 10^9$/L)	5.68 (4.91, 6.48)^{ns}	5.69 (4.91, 6.48)^{ns}	–0.09	0.926
	PLT ($\times 10^9$/L)	240.00 (207.00, 265.00)^{ns}	228.00 (195.00, 261.00)^{ns}	–1.46	0.145
	Hb (g/L)	127.70 (116.60, 137.20)^{ns}	129.80 (121.10, 135.80)^{ns}	–0.43	0.665
	ALT (U/L)	23.50 (19.30, 26.50)^{ns}	22.80 (19.90, 25.50)^{ns}	–0.92	0.359
	AST (U/L)	20.90 (17.50, 24.60)^{ns}	21.60 (18.90, 24.00)^{ns}	–0.32	0.749
	Scr (µmol/L)	67.20 (60.40, 72.70)^{ns}	68.30 (58.90, 74.50)^{ns}	–0.00	0.997
	BUN (mmol/L)	5.11 (4.62, 5.52)^{ns}	5.11 (4.66, 5.87)^{ns}	–0.60	0.552

Notes: Data are expressed as M (Q1, Q3). Continuous variables were analyzed using the Mann-Whitney U test. The "ns" denotes not significant when compared with before treatment.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Hb, hemoglobin; PLT, platelet; Scr, serum creatinine; WBC, white blood cell.

paired signal conduction [15]. Sodium ferulate mitigates early-stage damage to dorsal root ganglion neurons and Schwann cells by scavenging free radicals, activating the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) signalling pathway, and reducing the release of pro-inflammatory factors [31]. Meanwhile, mecobalamin, as a key cofactor in nerve repair, directly contributes to the remyelination and structural regeneration of damaged axons by promoting the synthesis of nucleic acids, proteins, and phospholipids [23,32]. Thus, the combination therapy exerts a dual effect: sodium ferulate creates a conducive microenvironment for neural repair by suppressing oxidative and inflammatory responses, while mecobalamin directly facilitates the reconstruction of neural structure and functional recovery. This multi-target strategy, which simultaneously addresses both the etiology and repair mechanisms of OIPN, provides a rational mechanistic basis for the superior efficacy of the combination therapy over monotherapy.

In terms of neuroelectrophysiological outcomes, the MNCV and SNCV of the median and common peroneal nerves in the observation group were significantly higher than those in the control group at both 4 and 8 weeks post-treatment, with the improvement becoming more pronounced over time. These results further confirm the advantage of combination therapy in promoting neurological functional recovery. It is worth noting that significant between-group differences were observed as early as 4 weeks, suggesting a relatively rapid onset of benefit, which may facilitate early intervention in the progression of OIPN. These findings are consistent with previous experimental research; for instance, Zhang et al. [33] reported that ferulic acid significantly improved NCV in a rat model of sciatic nerve crush injury, an effect associated with the inhibition of oxidative stress and inflammatory responses. However, it is important to acknowledge the inherent limitations of NCV as a primary outcome measure. OIPN is characterized primarily as an axonal injury, and while NCV is a useful clinical indicator of large myelinated fiber function, it is influenced by multiple technical factors such as body temperature, recorded distance, and filter settings [18]. Furthermore, NCV lacks sufficient sensitivity to detect early or subtle axonal loss, which is a hallmark of OIPN pathology [13]. The observed improvements in NCV likely reflect enhanced function in remaining intact or recovering fibers. Future studies incorporating more direct and sensitive measures of axonal integrity, such as skin biopsy for intraepidermal nerve fiber density or corneal confocal microscopy, could provide complementary and more specific insights into the structural neuroprotective effects of the combination therapy.

Furthermore, the overall clinical efficacy rate in the observation group was significantly higher than that in the control group after 8 weeks of treatment (89.47% vs. 67.97%), and quality-of-life scores were significantly improved across all functional domains. This indicates that the combination therapy is not only effective in objective indicators but also significantly enhances patients' subjective well-being and daily living abilities, demonstrating high clinical utility. Quality-of-life assessment showed that the observation group had significantly higher scores than the control group in physical, role, cognitive, emotional, and social functioning. Previous studies have emphasized that OIPN often leads to reduced daily living capacity, emotional distress, and impaired social participation [34,35]. The marked improvements in emotional and social functioning observed in the observation group may therefore be attributed to the alleviation of neuropathic symptoms and a consequent reduction in psychological burden. In terms of safety, no significant differences were observed between the two groups in complete blood count or liver and kidney function indicators at any time points, indicating that the combination of sodium ferulate and methylcobalamin has a favorable safety profile and is suitable for clinical application.

Despite the promising results, several limitations of this study must be acknowledged. Firstly, the retrospective and non-randomized design inherently introduces the risk of selection bias and confounding by indication. Although baseline demographic and clinical characteristics were well-balanced between the two groups, it is possible that clinicians preferentially assigned patients with more severe or complex neuropathy symptoms to the combination therapy group based on clinical judgment. The presence of such unmeasured confounders (e.g., baseline neuropathic pain intensity, specific OIPN symptom distribution, or patient-specific pain tolerance) could influence the outcomes. No statistical methods, such as propensity score matching, were employed to adjust for these potential biases, which is a limitation of the present analysis. Secondly, the assessments for quality of life (EORTC QLQ-C30) and neurotoxicity grading (NCI-CTCAE) may have been influenced by subjectivity. These assessments were conducted by clinicians involved in patient care who were not blinded to the treatment allocation. This lack of blinding creates a potential for assessment bias, as knowledge of the treatment group might unconsciously influence scoring. Thirdly, the study's 8-week treatment and evaluation period captures only short-term efficacy and safety, limiting insights into long-term outcomes. OIPN often has a persistent or fluctuating course, and some patients experience symptoms long after chemotherapy cessation [15]. The lack of long-term follow-up data limits our ability to draw conclusions about the sustained benefits, potential for relapse, and long-term safety profile of the combination therapy. Hence, future prospective, randomized, double-blind, placebo-controlled trials employing more sensitive and objective outcome measures of axonal integrity, along with extended follow-up periods, are warranted to confirm our findings and evaluate the long-term dynamics of OIPN under this combination regimen.

5. Conclusion

The combination of sodium ferulate with methylcobalamin for treating oxaliplatin-induced peripheral neuropathy in CRC patients significantly reduces neurotoxicity grades, improves neurological function, enhances clinical efficacy and quality of life, and demonstrates a favorable safety profile without increasing the risk of adverse reactions. This combination therapy exhibits a safe and effective option for the prevention and treatment of OIPN in clinical practice and merits further evaluation and broader application.

Key Points

• The combination of sodium ferulate with methylcobalamin demonstrated superior efficacy over methylcobalamin monotherapy in mitigating neurotoxicity severity and improving nerve conduction velocity in patients with oxaliplatin-induced peripheral neuropathy.

• Combination therapy achieved a significantly higher overall clinical efficacy rate and produced marked improvements across all quality-of-life domains.

• The observed therapeutic synergy is likely attributed to sodium ferulate's antioxidant and anti-inflammatory actions, complementing methylcobalamin's role in promoting nerve repair and regeneration.

• The combination regimen exhibited a favorable safety profile comparable to monotherapy, supporting its potential for broader clinical application.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

BM and RC conceived and designed the study. BM, LW, HH, and JC acquired the clinical data. ZJ performed the data analysis and interpretation. All authors contributed to drafting the work and revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors agreed to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

All procedures complied with the Declaration of Helsinki. The study was approved by the medical Ethics Committee of Qianxi People's Hospital (Number: 20220803). Written informed consent was obtained from all patients before enrollment.

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Conflicts of Interest

The authors declare no conflicts of interest.

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