Clinical Study on the Treatment of Fibromyalgia Syndrome Utilizing Ozone Pain Point Injection Combined with Duloxetine

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Abstract [**Objectives**] To investigate the clinical efficacy of duloxetine combined with ozone pain point injection for the treatment of fibromyalgia (FM) and assess the effects of this combination therapy on pain, depression, and sleep disorders. [**Methods**] A randomized controlled crossover design was employed in this study. Sixty inpatients diagnosed with FM were allocated into three groups: the duloxetine group, the ozone group, and the combination therapy group, with each group consisting of 20 participants. The treatment duration was set at 4 weeks. The Visual Analogue Scale (VAS), the Fibromyalgia Impact Questionnaire (FIQ), the Hamilton Depression Scale (HAMD), the Pittsburgh Sleep Quality Index (PSQI), and the number of tender points were assessed prior to treatment, 2 weeks post treatment, and 4 weeks post treatment. [**Results**] There were no statistically significant differences in various indicators among the three groups of patients prior to treatment. Following treatment, the VAS, FIQ, HAMD, PSQI, and the number of tender points in all three groups exhibited significant improvements ($P<0.05$). Notably, the combination therapy group demonstrated the most substantial reductions in each score, surpassing the improvements observed in the single application group ($P<0.05$). [**Conclusions**] Duloxetine combined with ozone pain point injection demonstrates a synergistic effect in alleviating pain, reducing depression, and enhancing sleep quality in patients with FM. This combination therapy exhibits superior efficacy compared to monotherapy and holds significant potential for clinical application.

Key words Fibromyalgia (FM), Duloxetine, Ozone injection, Pain, Depression, Sleep quality

1 Introduction

Fibromyalgia (FM) is a prevalent chronic condition encountered in clinical practice, primarily characterized by widespread muscular pain and discomfort throughout the body. This condition is frequently associated with a range of emotional disorders, including depression, anxiety, cognitive impairment, and sleep disorders[1]. Many patients also report experiencing various physical discomforts, including irritable bowel syndrome, excessive sweating, headaches, *etc.*[2]. In the United States, FM affects approximately 5 million individuals, accounting for about 1.6% of the total population, with a predominance in women[3]. Duloxetine is a tricyclic reuptake inhibitor that has received approval from the Food and Drug Administration (FDA). Its primary mechanism of action involves the inhibition of the reuptake of 5-hydroxytryptamine (5-HT) and norepinephrine (NE) by neurons, which results in elevated concentrations of these neurotransmitters in the central nervous system and spinal cord. Duloxetine is indicated for the treatment of acute major depressive disorder, generalized anxiety disorder, peripheral neuropathic pain, and FM[4]. Ozone is a potent oxidizing agent characterized by highly unstable molecular structures, which can decompose to yield monatomic oxygen (O) and hydroxyl radicals (OH), both of which possess significant oxidizing capabilities. The primary functions of ozone include anti-inflammatory and anti-infective properties, analgesic effects, oxidation of cholesterol, enhancement of immune response, and provision of oxygen to ischemic tissues. The application of this treatment is prevalent in clinical practice for conditions such as atherosclerosis, hyperlipidemia, rheumatoid diseases, and various other systemic disorders. Nevertheless, owing to its benefits, including safety, convenience, and environmentally friendly treatment, the scope of its clinical indications has significantly broadened. Presently, it is extensively utilized within pain management departments for patients requiring nerve blocks and localized pain point injections.

Currently, amitriptyline is the primary treatment for FM, However, an increasing body of evidence suggests that duloxetine may be more effective and associated with fewer adverse effects. Patients with FM often exhibit a range of systemic manifestations, and there remains a deficiency of rigorous and reliable data regarding the efficacy of combination therapies. This clinical trial aimed to address the existing knowledge gap and fulfill clinical requirements by comparing the therapeutic effects of duloxetine, ozone pain point injection, and their combination in the treatment of FM.

2 Information and methods

2.1 General information The study received approval from the hospital's ethics committee and involved the selection of patients diagnosed with FM who were hospitalized in the Department of Neurological Rehabilitation at Shiyan Taihe Hospital in Hubei Province between July 2020 and July 2024. Following thorough communication and the acquisition of written consent, a total of 66 patients underwent drug and ozone pain point injections. The experimental process was ultimately completed, and a total of 60 patients were followed up. The age range of the participants was between 22 and 57 years, and the duration of the disease varied from

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2 to 8 years. The cohort consisted of 4 males and 56 females.

2.2 Diagnosis and exclusion criteria The diagnosis criteria included the presence of widespread, symmetrical, and fixed tender points throughout the body, with a minimum of 11 out of 18 points affected; the presence of sleep disorders; symptoms of irritability; gastrointestinal disturbances; excessive sweating; and a disease duration exceeding one year without the presence of any other organic diseases.

The exclusion criteria encompassed individuals with coexisting mental disorders and severe organic diseases (such as malignant tumors, neurological disorders, and other rheumatic diseases); pregnant and lactating women; individuals with ulcers of the digestive system or gastrointestinal bleeding; individuals with known allergies to the test drug or ozone, a history of alcohol or drug abuse, and those exhibiting insufficiencies in vital organ functions (such as liver or kidney dysfunction); and individuals with cardiovascular diseases. Individuals diagnosed with inflammatory, infectious, neoplastic, or autoimmune diseases were not eligible for participation in the study.

2.3 Treatment methods The study employed a crossover design. Participants were enrolled using a random number table method, followed by sequential randomization allocation. The subjects were randomly assigned to three groups: the duloxetine group (group D), the ozone injection group (group O), and the duloxetine-ozone injection group (group D + O), with each group consisting of 20 participants. The duration of the trial was one month. In group D, duloxetine was administered daily at a dosage of 60 mg, as recommended by the FDA. Group O received ozone (O_3) pain point injection treatment once every 3 d, totaling twice a week for 8 sessions. Each pain point was injected with 2 mL of a 30 μg/mL ozone solution. Group D + O underwent all of the aforementioned procedures.

During the treatment period, patients were prohibited from using other antidepressants, opioid analgesics, or non-steroidal anti-inflammatory drugs.

2.4 Efficacy evaluation The Visual Analogue Scale (VAS), the Fibromyalgia Impact Questionnaire (FIQ), and the number of tender points were assessed prior to treatment, 2 weeks post treatment, and 4 weeks post treatment. A physician from the mental health center was invited to assess the Hamilton Depression Scale (HAMD) and the Pittsburgh Sleep Quality Index (PSQI) in order to conduct a comprehensive evaluation of the therapeutic effects of each treatment group for FM. A higher VAS score indicates greater severity of the patient's pain. A higher FIQ score is associated with a poorer quality of life for patients. Similarly, an elevated HAMD score indicates an increased risk of depression. Furthermore, a higher PSQI score reflects a decline in sleep quality. The assessment of tender points was conducted by applying thumb pressure, approximately 4 kg, to the 18 designated tender point areas as outlined in the diagnosis criteria across the body.

2.5 Statistical processing The experimental data were presented as mean ± standard deviation ($\bar{x} \pm SD$) and analyzed utilizing SPSS 23.0 statistical software. A homogeneity of variance test was conducted to compare means among multiple sample groups, while one-way analysis of variance (ANOVA) was employed for comparisons between groups. Additionally, ANOVA of repeated measures was utilized for comparisons within groups. The Student-Newman-Keuls (SNK) method was applied to determine significant differences among the groups. A significance level of $\alpha = 0.05$ was established, with $P < 0.05$ considered statistically significant.

3 Results and analysis

3.1 General information There were no statistically significant differences in the general characteristics among the three groups, as presented in Table 1.

Table 1 Comparison of general information among the three groups of patients prior to treatment ($n = 20$)

Group	Age//year	Gender//case		Course of disease//year
		Male	Female	
D	38.70 ± 10.584	1	19	4.00 ± 1.298
O	39.20 ± 9.666	2	18	3.90 ± 1.518
D + O	39.05 ± 8.721	1	19	3.80 ± 1.609

3.2 Sensation of pain There was no statistically significant difference among the groups prior to treatment (Table 2). At both 2 weeks and 4 weeks post treatment, the VAS scores for each group were significantly lower than those recorded prior to treatment, with the differences being statistically significant ($F = 324.365$, $P < 0.05$). Additionally, the differences between the groups were also statistically significant ($F = 4.735$, $P < 0.05$). The number of tender points in each group post treatment was significantly lower than that observed prior to treatment, with a statistically significant difference ($F = 514.046$, $P < 0.05$). Additionally, the difference between the groups was also statistically significant ($F = 9.452$, $P < 0.05$). These findings suggest that the analgesic effect of the combination therapy is superior to that of monotherapy.

Table 2 Comparison of VAS scores and tender points of the three groups of patients prior to and following treatment ($n = 20$)

Group	Time	VAS	Number of tender points
D	Prior to treatment	5.20 ± 1.152	14.35 ± 2.303
	2 weeks post treatment	3.30 ± 1.129	10.35 ± 2.700
	4 weeks post treatment	4.20 ± 1.056	7.85 ± 2.720
O	Prior to treatment	5.45 ± 1.234	13.85 ± 2.41
	2 weeks post treatment	4.30 ± 1.218	12.25 ± 2.53
	4 weeks post treatment	4.45 ± 1.146	9.25 ± 2.149
D + O	Prior to treatment	5.40 ± 1.314	14.35 ± 2.254
	2 weeks post treatment	2.00 ± 1.124 *△	7.35 ± 1.631 *△
	4 weeks post treatment	2.80 ± 0.894 *△	5.35 ± 1.531 *△

NOTE * $P < 0.05$, compared to those prior to treatment; △ $P < 0.05$, compared to group D and group O. The same below.

3.3 Quality of life of patients There was no statistically significant difference among the groups prior to treatment. At both 2 weeks and 4 weeks post treatment, the FIQ scores for each group were significantly lower than those recorded prior to treatment, with the differences being statistically significant ($F = 324.365$, $P < 0.05$). Additionally, the differences observed between the groups were also statistically significant ($F = 4.735$, $P < 0.05$). The PSQI scores for each group were significantly lower following treatment compared to those recorded prior to treatment, with a statistically significant difference ($F = 121.349$, $P < 0.05$). Additionally, the differences between the groups were also statistically significant ($F = 12.304$, $P < 0.05$). These findings suggest that the combination therapy is more effective than monotherapy in enhancing the quality of life for patients, particularly in terms of improving sleep quality (Table 3).

3.4 Evaluation of depressive symptoms At the conclusion of the 4-week treatment, the HMMD scores for all three groups exhibited a statistically significant reduction compared to their pretreatment levels ($F = 1\,079.961$, $P < 0.05$). Notably, the group receiving duloxetine-ozone injections demonstrated a more pronounced antidepressant effect ($F = 5.089$, $P < 0.05$) (Table 3).

Table 3 Comparison of PSQI, FIQ and HAMD among the three groups of patients prior to and following treatment ($n = 20$)

Group	Time	PSQI	FIQ	HAMD
D	Prior to treatment	50.35 ± 7.118	12.20 ± 3.518	25.55 ± 5.610
	2 weeks post treatment	36.30 ± 7.406	10.35 ± 2.907	16.50 ± 4.149
	4 weeks post treatment	28.05 ± 7.119	10.75 ± 2.633	11.30 ± 2.958
O	Prior to treatment	49.70 ± 7.399	11.90 ± 2.918	26.00 ± 4.531
	2 weeks post treatment	31.55 ± 6.030	7.30 ± 2.716	15.10 ± 4.734
	4 weeks post treatment	24.00 ± 5.731	7.40 ± 2.371	10.25 ± 3.370
D + O	Prior to treatment	51.15 ± 6.885	12.00 ± 3.197	25.10 ± 5.340
	2 weeks post treatment	21.25 ± 6.680 *△	4.70 ± 2.055 *△	10.35 ± 3.066 *△
	4 weeks post treatment	17.40 ± 5.614 *△	4.15 ± 2.139 *△	6.95 ± 2.502 *△

4 Discussion

This study is the inaugural investigation into the combined use of duloxetine and ozone pain point injection for the treatment of patients with FM. The findings indicate that the group receiving the duloxetine-ozone pain point injection demonstrated superior outcomes compared to the group receiving a single application, particularly in terms of pain relief, sleep improvement, and enhancement of patients' quality of life. Patients diagnosed with FM predominantly exhibit symptoms of stiffness, pain, and discomfort in the muscles, accompanied by distinct fixed tender points throughout the body. Some researchers have proposed a theory regarding the "dysregulation of local tissue vasomotor function and dilation", positing that enhanced blood flow perfusion to the affected tissues may effectively alleviate muscle pain. A separate study indicated that the average nocturnal blood oxygen saturation levels in patients with FM were below 90%[5]. The author proposes a hypothesis suggesting that inadequate blood perfusion in localized tissues may result in elevated concentrations of interleukin-1 (IL-1), substance P, and other related compounds within these tissues and muscles, potentially contributing to the chronic and persistent pain experienced by patients. The localized administration of ozone has the potential to markedly enhance the oxygen supply to tissues, restore cellular function, and improve cellular oxygen metabolism. Consequently, the hypothesis was formulated that local ozone injection could substantially alleviate the localized pain symptoms experienced by patients with widespread FM. The findings of the study corroborated this hypothesis.

Shi Guoyang *et al.*[6] conducted a systematic review of the literature in 2016 and concluded that the pathogenesis of FM encompasses multiple disciplines, including the central nervous system, autonomic nervous system, neurotransmitters, hormonal secretion, immune system, genetics, and psychiatry. The neurotransmitter 5-HT and various cytokines, including IL-6 and IL-8, are significantly associated with the pathogenesis of FM. While this study offers clinical evidence supporting the use of duloxetine combined with ozone pain point injection for the treatment of FM, several limitations must be acknowledged. Specifically, the sample size was inadequate, the follow-up duration was brief, and the depth of the investigation was insufficient. In future clinical treatments, it is essential to increase the number of cases and conduct comprehensive cellular and molecular studies to investigate the pathogenesis of FM. In conclusion, this study has demonstrated that the combination of duloxetine and ozone pain point injection can effectively alleviate pain in patients with FM, significantly improve associated sleep disorders and depressive symptoms, and warrants promotion in clinical practice. In comparison to the traditional antidepressant amitriptyline, duloxetine is associated with a reduced incidence of side effects, but its higher cost may restrict its clinical application among FM patients to a certain degree. Conversely, the ozone pain point injection technique is noted for its safety, efficacy, and absence of adverse effects, making it highly favored among clinical patients. Patients diagnosed with FM experience chronic pain, which adversely affects their quality of life, limits social engagement, and contributes to a decline in self-esteem and self-actualization. This study demonstrates that a 4-week combination therapy not only significantly alleviated pain in FM patients but also resulted in notable improvements in depression and sleep disorders. Consequently, the combined application of these therapeutic approaches merits further clinical promotion.

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scesses, inhibit bacterial growth on the wound, shorten the course of the disease, and reduce the medical burden. It possesses advantages such as being economical, effective, safe, and easy to operate. It is recommended that future research focus on establishing standardized therapeutic regimen, validating efficacy through multicenter randomized controlled trials (RCTs), and simultaneously strengthening toxicological studies to ensure medication safety. Through an integrated Chinese and Western medicine strategy, it may be possible to effectively resolve the current predicament of antibiotic abuse and the increasing prevalence of drug-resistant bacteria.

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