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Original Article

Therapeutic effect of opioid analgesics combined with non-steroidal anti-inflammatory drugs on peripheral neuropathy and its influence on inflammatory factors

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Abstract: Objective: To study the therapeutic effect of opioid analgesics combined with non-steroidal anti-inflammatory drugs on peripheral neuropathy and inflammatory factors. Methods: Clinical data of 60 patients with peripheral neuropathy were collected and studied retrospectively. The patients were divided into Group A (30 cases, treated with tramadol combined with ibuprofen) and Group B (30 cases, treated with tramadol alone). The visual analogue scale (VAS) and numerical rating scale (NRS) pain scores were recorded before and 3, 7, 14 and 21 days after taking the medicine. The adverse reactions of nausea, vomiting, gastrointestinal disorder, dizziness, rash and lethargy were recorded within 21 days after taking the medicine. Blood samples were obtained from patients before and 3, 7, 14 and 21 days after taking medicine to detect the inflammatory factors IL-6, IL-1β and TNF-α. Results: VAS and NRS scores of patients in Group A were significantly lower than those of patients in Group B after 7, 14 and 21 days of treatment (all $P<0.05$), but there was no significant difference in VAS and NRS scores between the two groups after 3 days of treatment (all $P>0.05$). The incidence of gastrointestinal disturbance in Group A was significantly higher than that in Group B ($P<0.001$). There was no significant difference in IL-6, IL-1β and TNF-α between the two groups 3 days after treatment (all $P>0.05$), but after 7, 14 and 21 days of treatment, the levels of IL-6, IL-1β and TNF-α in Group A were significantly lower than those in Group B (all $P<0.05$). Conclusion: Opioid analgesics combined with non-steroidal anti-inflammatory drugs is better than opioid analgesics alone in the treatment of peripheral neuropathy, and brings no more adverse reactions except gastrointestinal disorders, so the combined treatment can be further promoted for clinical use.

Keywords: Tramadol, ibuprofen, peripheral neuropathy

Introduction

Peripheral neuropathy is the dysfunction of peripheral autonomic nerve, sensory and motor function and structure [1, 2]. With a complex pathogenesis, it can be caused by many diseases. Different diseases can induce different symptoms of peripheral neuropathy. Pain is one of the most common symptoms of peripheral neuropathy, but its cause is not clear at present. It may be due to the fact that nerve damage induced by peripheral neuropathy leads to abnormal discharge of damaged neurons and pain [3]. Pain, as the fifth vital sign of human beings, seriously compromises people's quality of life, so it is extremely important to alleviate pain to improve the quality of life of patients. The drugs used to treat pain mainly include opioids and non-steroidal anti-inflammatory drugs [4, 5]. These two categories of drugs have many subordinate drugs, while tramadol belongs to weak opioids. Compared with strong opioids, tramadol has fewer side effects, so it can be used as a drug for moderate pain. It also brings less addiction, so it is commonly used as oral drugs for clinical pain treatment. Ibuprofen belongs to non-steroidal anti-inflammatory drugs, with antipyretic, anti-inflammatory and analgesic effects. It acts on pain-specific receptors in the central nervous system, thus inhibiting central nerve conducting pain and smooth muscle spasm, which can relieve pain from both central and peripheral aspects [6]. Ibuprofen is a non-steroidal anti-inflammatory dr-

ug, with antipyretic, anti-inflammatory and analgesic effects, and can reduce the neuroinflammatory reaction and the damage of neurons and proteins [7]. In previous studies, symptomatic treatment was commonly applied for peripheral neuropathy, while the pain was treated with gabapentin or tricyclic antidepressants, which had plain treatment effect and obvious side effects, such as depression and decreased quality of life [1]. Tramadol and non-steroidal anti-inflammatory drugs were commonly used analgesics in clinic, with better analgesic effect, and combined treatment could reduce the side effects of single drugs. In this paper, the therapeutic effects of opioids combined with non-steroidal anti-inflammatory drugs on peripheral neuropathy and inflammatory factors were studied to explore the possible mechanism.

Materials and methods

General data

Altogether 60 patients with peripheral neuropathy pain from June 2019 to June 2020 were enrolled as research participants for this retrospective study. The patients were selected and divided into group A (30 cases, treated with tramadol combined with ibuprofen) and group B (30 cases, treated with tramadol alone).

Inclusion criteria: (1) Patients aged 18-65 years; (2) Patients confirmed with peripheral neuropathy, such as diabetic peripheral neuropathy [8], infectious peripheral neuropathy, vasculitis peripheral neuropathy or toxic peripheral neuropathy [9-11], and patients with pain caused by peripheral neuropathy; (3) Patients who had not been treated with opioid or non-steroidal anti-inflammatory drugs or other analgesic drugs within 2 weeks.

Exclusion criteria: (1) Patients with severe dysfunction of vital organs; (2) Those with a history of peptic ulcer or active bleeding in gastrointestinal tract; (3) Those allergic to the drugs or drug components used in this study; (4) Those with history of asthma; (5) Those who had mental related diseases or failed to cooperate with researchers. This study was approved by the medical ethics committee, and the informed consent forms were obtained from the patients and their families.

Treatment methods

Each patient in the two groups properly took drugs to treat other symptoms, such as drugs to control infection and blood sugar and improve other neurological symptoms. Patients in group A were given tramadol sustained-release tablets (Grünenthal GmbH, H2005-0224, 100 mg/tablet, 50 mg/time) and ibuprofen sustained-release tablets (Huizhou Daya Pharmaceutical Co., Ltd., H44025287, 0.3 g/tablet, 0.3 g/time), twice a day. Patients in group B were given tramadol sustained-release tablets (50 mg/time), twice a day.

Monitoring indicators

Main monitoring indicators: Visual analogue scale (VAS) of patients before taking medicine (T0) and 3(T1), 7(T2), 14(T3) and 21(T4) days after taking medicine was detected and recorded, and a long line (generally 10 cm) was drawn, with one end representing painless, and the other end representing severe pain. The patients were required to draw a cross line that can best reflect their pain level. The pain degree of the patient was determined according to the position of the cross line. The numerical rating scale (NRS) was applied, with 0-10 representing different degrees of pain, 0 for painless and 10 for severe pain. The patient was required to circle a number that can best represent the degree of pain. Enzyme-linked immunosorbent assay (ELISA) was used to detect the blood inflammatory factors including interleukin-6 (IL-6, Abcam, ab46042), interleukin-1β (IL-1β, Abcam, ab214025) and tumor necrosis factor-α (TNF-α, Abcam, ab181421) before medication (T0) and 3(T1), 7(T2), 14(T3) and 21(T4) days after medication.

Secondary monitoring indicators: The adverse reactions such as nausea, vomiting, gastrointestinal disorder, dizziness, rash and sleepiness in the two groups were monitored and recorded within 21 days after they took the medicine (adverse reaction rate = the number of patients with adverse reactions/the total number of patients × 100%).

Safety assessment

If the side effects of patients were obvious during treatment and there was no remission after treatment, the patients were treated with other drugs, and regarded as invalid cases.

Table 1. Comparison of general data ($\bar{x}$±sd)

Group/Project	Group A	Group B	t/χ^2	P
Age (years)	51.7±13.2	53.3±12.9	0.479	0.634
Gender (n)			0.268	0.605
Male	17	15		
Female	13	15		
BMI (kg/m^2)	20.85±2.13	21.42±2.37	0.978	0.331
Type of disease (n)			0.973	0.914
Diabetic peripheral neuropathy	16	17		
Infectious peripheral neuropathy	6	4		
Angiammatory peripheral neuropathy	3	2		
Toxic peripheral neuropathy	3	4		
Other	2	3		

Note: BMI: Body Mass Index.

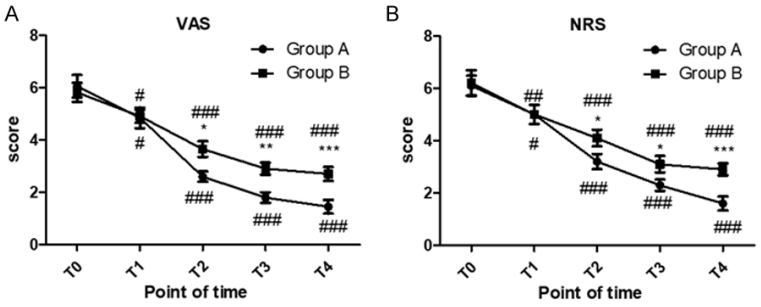

Figure 1. Comparisons of pain scores between the two groups. A: Comparison of VAS scores between the two groups. B: Comparison of NRS scores between the two groups. Compared with T0, #P<0.05, ##P<0.01, ###P< 0.001; compared with Group B, *P<0.05, **P<0.01, ***P<0.001. VAS: visual analogue scale; NRS: numerical rating scale.

Statistical methods

The experimental data were analyzed and visualized using SPSS19.0 and Graphpad Prism5. The measurement data were represented as mean ± standard deviation ($\bar{x}$±SD). The independent sample t test was used for comparison between the two groups, and repeated measurement variance analysis followed by Bonferroni post-hoc test was used for comparison between each time point. Counting data were expressed by cases (%). χ^2 test was used for comparison among groups, and rank sum test was used for rank variables. P<0.05 indicated that the difference was statistically significant.

Results

Comparison of general data

There was no significant difference in age, gender, body mass index (BMI) and disease types between the two groups (all P>0.05; **Table 1**).

Comparison of pain scores

There was no difference in VAS and NRS scores between the two groups before medication (T0) and 3 days (T1) after medication (all P>0.05), while VAS and NRS scores of the two groups were significantly lower at 3 days (T1), 7 days (T2), 14 days (T3) and 21 days (T4) after medication (all P< 0.05). At T2, T3 and T4, the scores of Group A were significantly lower than those of Group B (all P<0.05; **Figure 1**).

Comparison of inflammatory factors

There was no significant difference in the concentrations of three inflammatory factors between the two groups at T0 and T1 (all P>0.05). The concentrations of IL-6, IL-1β and TNF-α at T1, T2, T3 and T4 were significantly lower than those before treatment (all P<0.05), while those in group A were significantly lower than those in group B at T2, T3 and T4 (all P<0.05; **Tables 2**-**4**).

Comparison of adverse reactions

There was no significant difference in nausea, vomiting, dizziness, rash and sleepiness bet ween the two groups (all P>0.05), but the gastrointestinal dysfunction reaction in Group A was significantly more than that in Group B (P<0.001; **Table 5**).

Table 2. Comparison of IL-6 concentration between the two groups ($\bar{x}$±sd)

Group/Time	T0	T1	T2	T3	T4
Group A (pg/mL)	25.43±7.51	21.41±7.67*	14.55±6.24***	11.16±6.58***	7.73±7.46***
Group B (pg/mL)	26.88±7.46	20.79±7.59*	18.31±7.04***	16.71±7.26***	14.63±6.52***
t	0.750	0.315	2.190	3.102	3.815
P	0.456	0.754	0.033	0.003	0.000

Note: Compared with T0, *P<0.05,***P<0.001.

Table 3. Comparison of IL-1β concentration between the two groups ($\bar{x}$±sd)

Group/Time	T0	T1	T2	T3	T4
Group A (pg/mL)	27.37±8.82	22.57±7.18*	14.93±7.71***	11.48±6.14***	8.27±7.32***
Group B (pg/mL)	27.59±9.25	21.11±8.54*	19.25±8.63***	17.88±7.33***	15.59±6.85***
t	0.094	0.717	2.045	3.666	3.999
P	0.925	0.476	0.045	0.001	0.000

Note: Compared with T0, *P<0.05, ***P<0.001.

Table 4. Comparison of TNF-α concentration between the two groups ($\bar{x}$±sd)

Group/Time	T0	T1	T2	T3	T4
Group A (pg/mL)	33.18±8.66	26.43±7.26**	20.18±6.48***	14.06±7.35***	12.27±6.33***
Group B (pg/mL)	31.77±8.74	26.11±8.47*	24.44±7.07***	21.49±8.15***	17.41±7.04***
t	0.628	0.157	2.433	3.708	2.974
P	0.533	0.876	0.018	0.000	0.004

Note: Compared with T0, *P<0.05, **P<0.01, ***P<0.001.

Table 5. Comparison of incidence of adverse reactions (n, %)

Group/Time	Group A	Group B	χ^2	P
Nausea	7 (23.33)	9 (30.00)	1.138	0.286
Vomiting	5 (16.67)	6 (20.00)	0.370	0.543
Dizziness	11 (36.67)	10 (33.33)	0.245	0.621
Rash	4 (13.33)	3 (10.00)	0.538	0.463
Lethargy	15 (50.00)	14 (46.67)	0.222	0.638
Gastrointestinal disorders	12 (40.00)	5 (16.67)	13.402	<0.001

Discussion

Peripheral neuropathy is a lesion of the peripheral nervous system, and its clinical symptoms are complex, including movement and sensory disorders, ataxia and tremor, even deformity and disability in severe cases [12-14]. In particular, it can cause physical pain. Many patients with peripheral neuropathy have no obvious symptoms in the early stage, and pain that seriously affects the patient's body and mind may be one of the earliest symptoms [15, 16]. Therefore, the treatment of pain is crucial for treating peripheral neuropathy. There are many analgesics in clinical practice, and they are mainly classified into opioids and non-steroids [17, 18]. With antipyretic, analgesic and anti-inflammatory effects, are widely used against fever, rheumatism, and chronic pain, and in prevention of cardiovascular and cerebrovascular diseases. Their side effects are obviously less than those of opioids in the treatment of pain, and there is almost no inhibition of respiration and circulation, so they are widely used in clinic. When opioids are used with non-steroidal anti-inflammatory drugs, their dosage can be reduced, and thus it brings fewer side effects [17, 18].

The secretion of proinflammatory factors increases obviously when inflammation occurs in the body. IL-6, IL-1β and TNF-α are mainly produced by macrophages, but also by monocytes [19-21]. When inflammation occurs in the body, the secretion of these proinflammatory factors increases, and it also increases in tuberculosis,

autoimmune diseases, tumors and other diseases. This research explored the role of proinflammatory factors in peripheral neuropathy. Studies have confirmed that tramadol has a therapeutic effect on peripheral neuralgia caused by diabetes [22]. It can significantly relieve the pain caused by diabetic neuropathy, but its mechanism is not clear. This paper found that both tramadol alone and tramadol combined with ibuprofen can treat the pain caused by peripheral neuropathy, which not only acts in diabetes, but also is useful for other types of peripheral neuropathy. It can also reduce the contents of IL-6, IL-1β and TNF-α in peripheral neuropathy. The content of proinflammatory factors in patients with peripheral neuropathy increased, which may be caused by the disease, and inflammation may be one of the mechanisms causing pain in patients with peripheral neuropathy. When the inflammation was treated, the pain was relieved. On the third day of the treatment, the treatment effect of the two groups was similar, and the pain response was better than that before treatment, but there was no significant difference between them. After seven days of treatment, the treatment effect of tramadol combined with ibuprofen was more obvious, the pain score was obviously reduced, and the reaction of proinflammatory factors was reduced. On the third day of treatment, there was no significant difference in the degree of reduction between the two groups, but it was more obvious after seven days of treatment, indicating that the anti-inflammatory effect of ibuprofen reduced the content of inflammatory factors. Therefore, it could verify that tramadol combined with ibuprofen had a good therapeutic effect on peripheral neuropathy pain, which is obviously better than tramadol alone, and the treatment of pain obviously improved the quality of life of patients. The better effect of pain treatment indicates higher quality of life of patients, and there is no significant difference in side effects between the two groups except gastrointestinal disorders. This result proved that the combined medication did not significantly increase side effects, but drugs that protect gastrointestinal functions are needed.

In addition, our research results showed that the VAS and NRS scores of the patients in the two groups after treatment were significantly decreased than those before treatment, and the decrease in Group A was more obvious than that in Group B. This shows that tramadol and ibuprofen have a good effect on the pain symptoms of patients with peripheral neuropathy, and the combined use can significantly increase the curative effect.

There are still many shortcomings in this study. Due to time limitations, this study only collected the data of 21 days after treatment, so it is unclear whether the combined treatment can keep the therapeutic effect significantly better than tramadol alone in a longer period of treatment, and whether the long-term treatment will significantly increase the side effects of gastrointestinal disorders and even affect the daily life of patients. We did not reduce tramadol in the combined treatment group, so whether tramadol can still achieve good therapeutic effect after reduction needs further study. If tramadol combined with ibuprofen can still achieve good therapeutic effect, the advantages of combined treatment can be truly proved. This study only confirmed that tramadol combined with ibuprofen can reduce inflammatory factors *in vivo*, but the specific mechanism of reducing inflammatory factors was not studied, which also needs further study.

In conclusion, tramadol combined with ibuprofen has a good effect in the treatment of peripheral neuropathic pain, and its mechanism may be related to further reduction in content of inflammatory factors *in vivo*, but gastrointestinal protective drugs are needed during the application.

Disclosure of conflict of interest

None.

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