Research Paper

Comparative Study on Analgesic Effect, Sleep Quality and Safety of Duloxetine Combined with Pregabalin in the Treatment of Postherpetic Neuralgia

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The main objective of this study is to determine the analgesic effect, sleep quality and safety of duloxetine combined with pregabalin in the treatment of postherpetic neuralgia. The study participants compromised 90 postherpetic neuralgia patients, who were divided into two groups with 45 patients in each group. Group A (n=45) took duloxetine combined with pregabalin, and group B (n=45) took pregabalin only and the cycle was 12 w. The analgesic effect (nerve sensory conduction velocity, visual analogue scale score, verbal rating scale score), sleep quality (Pittsburgh sleep quality index score) and adverse drug reactions were compared between the two groups. After treatment, the values of various indexes of nerve sensory conduction velocity in group A were higher than those in group B ($p<0.05$), the scores of visual analogue scale and verbal rating scale in group A were lower than those in group B ($p<0.05$). The scores of various indexes of Pittsburgh sleep quality index in group A were lower than those in group B ($p<0.05$) and the incidence of adverse drug reactions was slightly higher than that of group B ($p>0.05$). Duloxetine combined with pregabalin has good analgesic effect in the treatment of postherpetic neuralgia, and has a significant effect on improving sleep quality with high safety.

Key words: Duloxetine, pregabalin, analgesic effect, adverse drug reactions, sleep quality

Postherpetic Neuralgia (PHN) is one of the most common complications of herpes zoster. Its clinical manifestations are tingling, burning, drilling and other neuropathic pain manifestations, which have seriously affected the lives of patients. PHN mostly occurs in middle-aged and elderly people, and the age is generally over 50 y old. Herpes zoster is the main cause of PHN and about 20 % of patients with herpes zoster will develop PHN[1]. The pathogenesis of PHN is still unclear and it is mainly believed that it is related to the decline of immune function. Stress, other diseases, drugs, genetics and neuropathological changes, etc. may also cause this disease. The pain range of PHN usually occurs on the skin of the herpes zoster lesion area and extends to the other areas, which can easily cause depression and sleep disturbance in patients[2]. The treatment methods for PHN mainly include drug therapy, physical therapy, nerve block therapy, nerve stimulation therapy and so on. Drug therapy is divided into analgesics, antidepressants, anticonvulsants, local anesthetics, antiviral drugs and so on. Analgesic drugs are mainly opioid and non-opioid. Antidepressants are mainly tricyclic antidepressants and Selective Serotonin Reuptake Inhibitors (SSRIs), which can relieve pain and depression. Pregabalin, a representative anticonvulsant drug, acts on the central nervous system to relieve pain and convulsions. Local anesthetics include lidocaine, bupivacaine, etc., which relieve local pain. Antiviral drugs such as acyclovir and valacyclovir hydrochloride can inhibit the replication of herpes zoster virus and prevent the virus from reactivating. While duloxetine belongs to the antidepressant class of drugs and an SSRI, it can relieve symptoms of depression and relieve nerve pain. It relieves nerve pain by increasing the concentration of serotonin. Pregabalin reduces the excitability of neurons by inhibiting the release of calcium ion, so as to relieve symptoms such as neuralgia and convulsions. In this study, duloxetine and pregabalin were used as research drugs, and were divided into a combined drug group and a single drug group, trying to compare the analgesic effect, sleep quality and drug safety of different drug regimens on PHN.

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MATERIALS AND METHODS

General information:

The data of this study come from 90 patients with PHN admitted to our hospital from June 2021 to June 2022. They were divided into group A and group B by odd-even grouping method, with 45 cases in each group. The average age of group A was (57.28±5.76) y old and the average disease duration was (6.92±1.84) w. The average age of group B was (57.32±5.75) y old and the average disease duration was (6.91±1.83) w. There was no significant difference in the basic data between the two groups ($p>0.05$).

Inclusion criteria:

Patients who meet the diagnostic criteria of herpes zoster and symptoms of nerve pain after herpes healing; Visual Analogue Scale (VAS) score≥4 points; all the patients understand the purpose of this study and sign the informed consent.

Exclusion criteria:

Nerve pain caused by other reasons; patients who received other nerve pain-related surgical treatment; patients who received nerve pain-related drug treatment or other methods of treatment before seeing the doctor; patients with heart and liver function diseases and patients with severe skin diseases are excluded from this study.

Research drugs:

Duloxetine is an enteric-coated capsule which was manufactured by Shi Yao Group Ouyi Pharmaceutical Co., Ltd. (Approval number: SinopOD H20203350) with specification 20 mg×30 capsules.

Pregabalin is a capsule which was manufactured by Qilu Pharmaceutical (Hainan) Co., Ltd. (Approval number: Sinopecial code H20203040) with specification 75 mg×32 capsules.

Drug usage and dosage:

Patients of group B were instructed to take 75 mg pregabalin daily before going to bed and after 3 d, take a 75 mg tablet in the morning, and maintain the dose. The total treatment cycle was 12 w.

Patients of group A were instructed to take 20 mg tablet of duloxetine before breakfast, increasing the dose to 40 mg after 3 d, and increasing to 60 mg after 3 d and maintaining the dose. Along with duloxetine, patients were instructed to take pregabalin with dose similar to group B and the duration of medication was 12 w.

Research methods:

During the hospitalization, the patients were visually observed using the scoring table, and the drug effect of the patients was observed through regular outpatient review or telephone follow-up after discharge. The study time points were before medication, 4 w after medication and after medication. The analgesic effect includes nerve sensory conduction velocity, VAS score and Verbal Rating Scale (VRS) score; sleep quality assessment include Pittsburgh Sleep Quality Index (PSQI) score and adverse drug reactions were compared between the two groups.

Research indicators:

The analgesic effect was evaluated by nerve sensory conduction velocity, VAS score and VRS score. Nerve sensory conduction velocity includes Median Nerve sensory Conduction Velocity (MNCV), Ulnar Nerve sensory Conduction Velocity (UNCV) and common Peroneal Nerve sensory Conduction Velocity (PNCV). Generally speaking, the nerve conduction velocity is between 0.1 and 120 m/s. The faster the conduction velocity, the better the recovery effect of nerve conduction velocity.

The full score of VAS is 10 points where score of 0 means no pain; 1-3 means mild pain; 4-6 means more pain and affects sleep and 7-10 means very painful which affects eating and sleeping. A VAS score of ≤3 was considered pain-free.

The VRS score is a method for self-assessment of pain by patients. Choose a number from 1-10 to represent their own pain status, 1 means no pain and 10 means the most intense pain.

The sleep quality assessment method mainly uses the PSQI to score. The lower the score of each index, the higher the quality of sleep. In addition, it is necessary to examine the patient's wake-up time and the number of wake-up times.

The adverse drug reactions of the two groups of patients were recorded. Adverse drug reactions are divided into serious adverse drug reactions and general adverse drug reactions. Serious drug reactions that may occur in this study include thrombocytopenia, seizures, severe rash, disturbance of consciousness, generalized edema and dyspnea. General adverse

drug reactions that may occur in this study include dizziness, dry mouth, nausea, drowsiness, muscle pain, fatigue, constipation and joint pain, etc.

Statistical analysis:

The data involved in this study was processed using Statistical Package for Social Sciences (SPSS) 22.0 statistical software. The t-test or Chi-square (χ^2) test was performed to compare the results and $p<0.05$ was considered as statistically significant difference.

RESULTS AND DISCUSSION

There was no significant difference in the indexes of nerve sensory conduction velocity between A and B groups before treatment. After 4 w of medication and after the end of medication, all the indicators in group A were higher than those in group B ($p<0.05$) and the difference were statistically significant (Table 1).

There was no significant difference in VAS and VRS scores between the two groups before treatment. After 4 w of medication and after the end of medication, the VAS and VRS scores of patients in group A were significantly lower than those in group B ($p<0.05$) (Table 2 and Table 3).

Before medication, there was no significant difference in the comparison of wake-up time and number of times of waking up between A and B groups. After 4 w of treatment and after the end of the treatment, the time to wake up in group A was significantly lower than that in group B, and the number of times of waking up was significantly lower than that in group B ($p<0.05$) (Table 4).

Before treatment, there was no significant difference in each factor of PSQI between group A and group B ($p>0.05$). After 4 w of treatment and after the end of the treatment, the scores of each factor of PSQI in group A were significantly lower than those in group B ($p<0.05$) (Table 5).

There were no serious adverse drug reactions in the two groups of patients. There were 7 patients with general adverse drug reactions in group A and 6 patients with general adverse drug reactions in group B. There was no significant difference between the two groups ($p>0.05$) (Table 6).

TABLE 1: COMPARISON OF NERVE SENSORY CONDUCTION VELOCITY AT DIFFERENT TIME POINTS BETWEEN THE TWO GROUPS OF PATIENTS (x̄±s, M/S)

Study time points	Group	MNCV	UNCV	PNCV
Before medication	A (n=45)	29.17±2.42	28.28±2.33	27.86±2.34
	B (n=45)	29.26±2.41	28.19±2.32	27.91±2.33
t		0.436	0.422	0.417
p		>0.05	>0.05	>0.05
Medication for 4 w	A (n=45)	41.32±3.28	38.61±3.41	36.69±2.96
	B (n=45)	36.24±3.17	34.43±3.18	34.58±2.87
t		2.186	2.221	1.964
p		<0.05	<0.05	<0.05
After medication	A (n=45)	51.58±4.08	50.12±4.12	48.37±4.07
	B (n=45)	44.59±3.96	43.28±3.88	41.32±3.89
t		2.869	2.764	2.935
p		<0.05	<0.05	<0.05

TABLE 2: COMPARISON OF VAS SCORES BETWEEN THE TWO GROUPS AT DIFFERENT TIME POINTS (x̄±s, POINTS)

Group (n=45)	Before medication	Medication for 4 w	After medication
A	7.49±0.61	4.13±0.35	2.86±0.31
B	7.48±0.61	6.02±0.42	4.23±0.39
t	0.096	3.242	3.462
p	>0.05	<0.05	<0.05

TABLE 3: COMPARISON OF VRS SCORES BETWEEN THE TWO GROUPS AT DIFFERENT TIME POINTS (x̄±s, POINTS)

Group (n=45)	Before medication	Medication for 4 w	After medication
A	4.19±0.32	1.86±0.25	0.62±0.08
B	4.18±0.32	2.11±0.26	1.21±0.09
t	0.108	2.178	4.625
p	>0.05	<0.05	<0.05

TABLE 4: COMPARISON OF SLEEP QUALITY BEFORE AND AFTER TREATMENT IN TWO GROUPS OF PATIENTS (x̄±s)

Group (n=45)	Wake up time (min)			Wake up times (frequency)		
	Before medication	Medication for 4 w	After medication	Before medication	Medication for 4 w	After medication
A	82.16±8.32	32.28±3.81	23.56±2.52	4.91±0.41	2.92±0.22	1.93±0.11
B	82.32±8.33	46.72±4.23	33.48±3.47	4.89±0.41	3.61±0.31	2.93±0.21
t	0.121	2.364	4.128	0.119	2.086	2.683
p	>0.05	<0.05	<0.05	>0.05	<0.05	<0.05

TABLE 5: COMPARISON OF PSQI SCORES BETWEEN THE TWO GROUPS OF PATIENTS AT DIFFERENT TIME POINTS (x̄±s, POINTS)

Factors	Group A			Group B		
	Before medication	Medication for 4 w	After medication	Before medication	Medication for 4 w	After medication
Sleep quality	2.99±0.23	1.79±0.2^{b1}	0.56±0.06^{b1}	2.98±0.23	2.11±0.21^{b}	1.24±0.11^{b}
Bedtime	3.01±0.26	2.13±0.21^{b1}	1.17±0.08^{b1}	3.02±0.25	2.38±0.22^{b}	1.46±0.13^{b}
Sleeping time	2.92±0.24	1.91±0.19^{b1}	0.93±0.08^{b1}	2.93±0.24	2.13±0.18^{b}	1.36±0.12^{b}
Sleep efficiency	2.96±0.23	1.81±0.16^{b1}	1.01±0.07^{b1}	2.97±0.23	2.15±0.21^{b}	1.41±0.13^{b}
Sleep disorder	3.02±0.27	1.91±0.22^{b1}	1.13±0.11^{b1}	3.01±0.27	2.25±0.22^{b}	1.51±0.14^{b}
Hypnotic drugs	2.81±0.26	1.78±0.18^{b1}	0.82±0.07^{b1}	2.82±0.26	1.91±0.18^{b}	1.18±0.09^{b}
Day function	2.71±0.24	1.61±0.15^{b1}	0.81±0.07^{b1}	2.72±0.24	1.86±0.19^{b}	1.08±0.1^{b}
PSQI total score	20.41±0.38	12.92±0.29^{b1}	6.44±0.19^{b1}	20.43±0.39	14.78±0.31^{b}	9.22±0.15^{b}

Note: Compared with before medication, $^{b}p<0.05$ and compared with group B at the same time point, $^{1}p<0.05$

TABLE 6: COMPARISON OF ADVERSE DRUG REACTIONS IN TWO GROUPS OF PATIENTS (x̄±s, NUMBER OF CASES)

Group	n	Serious adverse drug reactions	General adverse drug reactions	Total incidence (%)
A	45	0	7 (15.56)	15.55
B	45	0	6 (13.33)	13.33
χ^2				0.829
p				>0.05

PHN refers to the disease in which the neuralgia persists after the herpes zoster rash has subsided and the pain often lasts for more than 1 mo. It is a refractory and intractable neuropathic pain and is the most common complication of herpes zoster. When PHN occurs, it must be treated in time, because the longer the course of the disease, the more difficult it is to treat, especially if the course of the disease exceeds 3 y or more, the difficulty of clinical treatment increases significantly. Shingles is an infection caused by the varicella-zoster virus, usually manifested as a shingles-like rash and pain. PHN belongs to the pain caused by neuroinflammation and nerve injury caused by herpes zoster virus invading ganglion cells[3]. This pain lasts for a long time, up to several months or even years, which can cause great inconvenience to the life of the patient. Studies have shown that this kind of pain is often persistent pain manifested by ectopic pathways and hyperalgesia, which not only affects the patient's sleep quality, hinders the activities of daily life, but also seriously reduces the patient's living standard[4]. Some researchers believe that the occurrence of PHN is due to peripheral sensitization[5]. The virus will be revived, so that new virus particles or virus products can be transported to the spinal nerve or brain nerve and to other sensory neurons innervated areas, thereby triggering neuroinflammatory response, nerve damage, nerve necrosis and sensory neuron function loss or scarring eventually results in painful sensations of the damaged ganglion and the area it innervates. Some researchers also believe that PHN is related to central sensitization[6]. After the central nervous system is damaged, the threshold of its action potential is reduced and the pain that was not felt before will be felt at this moment i.e., the pain is more significant. Other researchers believe that PHN is related to poor afferent conduction[7]. When viral damage causes loss of peripheral nociceptors, these fibers connect to secondary neurons and neurons appear to compensate for the pain of the original peripheral nociceptors. Studies have shown that PHN is associated with the patient's own immune response, in which the immune system attacks nervous tissue[8]. The incidence of PHN is closely related to age, showing a positive correlation. The immune function of elderly patients continues to decline and their nerve repair ability also declines. The time for nerve repair is longer and the probability of developing into PHN is higher.

For the treatment of PHN, the most convenient therapy is drug therapy. Both duloxetine and pregabalin are first-line drugs. Duloxetine is an antidepressant drug that can simultaneously inhibit the reuptake of 5-Hydroxytryptamine (5-HT) and Norepinephrine (NE) in the synaptic cleft and it can increase the concentration of the two transmitters between synapses in the central nervous system[9]. As the key transmitters of the central nervous system, 5-HT and NE can prevent the transmission of peripheral nociceptive stimuli to upper neurons and this process has an analgesic effect. Duloxetine also acts on the cerebral cortex, which improves the regulation of the cerebral cortex on emotion and pain, thereby enhancing the body's tolerance to pain and improving sleep quality. Studies have shown that compared with tricyclic depressants, the biggest advantage of duloxetine is that it is a highly selective receptor blocker with high safety and low side effects[10]. In chronic pain state, the inhibitory effect of duloxetine is assumed to decrease or disappear and its descending pain regulation system realizes the transition from inhibition to facilitation. As noted by the investigators, duloxetine reduces persistent pain perception[11]. Because of the high selectivity of the receptors, there are few side effects and these side effects such as nausea and constipation are tolerable by patients, so they will not stop the intake of drug because of these side effects[12]. NE has the effect of promoting wakefulness and serotonin is closely related to sleep. Duloxetine can affect these two neurotransmitters, thereby achieving the purpose of regulating sleep cycle and sleep quality. In addition, duloxetine, as the first-line antidepressant drug, can relieve the anxiety of patients, which is also conducive to improving the quality of sleep of patients.

Pregabalin is an antiepileptic and analgesic drug commonly used in the treatment of neuropathic pain and pain caused by peripheral neuropathy. Pregabalin is a Gamma-Aminobutyric Acid (GABA) drug and its pharmacological mechanism is to reduce pain by increasing the level of GABA in the central nervous system. As a neurotransmitter, GABA can inhibit the action of neurons to reduce the perception of pain[13]. The first target in the pharmacological mechanism of pregabalin is the GABA receptor. This receptor can be divided into two classes such as GABA-A and GABA-B. As an ion channel, GABA-A can transport chloride ions into neurons to inhibit neuron activity. As a G protein-coupled receptor, GABA-B relies on inhibiting the activity of adenylate cyclase, reduces the concentration of cyclic Adenosine

Monophosphate (cAMP) and reduces the activity of neurons by inhibiting the entry of calcium ions from extracellular into neurons[14]. Studies have shown that pregabalin can affect the pathway of glutamate metabolism[15]. As a key neurotransmitter in the central nervous system, glutamate is involved in the process of pain transmission or sensory processing[16]. Pregabalin can inhibit the activity of glutamate transaminase and prevent the synthesis of glutamate. In addition, pregabalin can also affect calcium ion channels. As a key signaling molecule in the central nervous system, calcium ions participate in the process of neuron excitation and transmission[17]. Pregabalin reduces the excitability of neurons by inhibiting the activity of calcium ion channels, so that the pain perception of patients is reduced. Pregabalin inhibits NE and calcium ion channels, which can reduce the excitability of neurons, thereby improving sleep quality. Studies have shown that pregabalin has some side effects, such as dizziness, drowsiness and fatigue, etc.[18].

Based on the above analysis of the pharmacological mechanism of duloxetine and pregabalin, a basic conclusion can be drawn that both have the effects of analgesia and improves sleep quality. The side effects of both drugs are relatively low and there are no serious adverse side effects. In this study, the dosage of the two drugs showed less-more-less, the main reason is that the first low dose is to increase the patient's tolerance to the drug and then the dose is increased to improve the curative effect of the drug, and finally the dose is reduced to prevent the occurrence of drug addiction after stopping the drug. In this study, the nerve sensory conduction velocity of patients in group A was faster at different time points after medication. It is generally believed that the faster nerve sensory conduction may make the patient's pain response faster. But in this study, the researchers tended to have faster nerve sensory conduction and better recovery of nerve function. The different medications of the two groups also showed that the nerve sensory conduction velocity of the patients after the medication was faster than that before the medication. Both VAS and VRS scores are self-perceived assessment scores, which are related to mood, cognition, pain tolerance, education level, etc. It is even said that for the same level of pain, the VAS scores and VRS scores given by different people vary greatly. The nerve sensory conduction velocity is objective and its research value is even greater. In this study, the VAS scores and VRS scores of patients in group A were lower than those in group B at different time points after treatment. This shows that the combined drug has a lower pain score and better analgesic effect. In this study, the sleep quality of patients in group A was better than that of patients in group B, which may be related to the antidepressant effect of duloxetine. In this study, no serious adverse drug reactions occurred in the two groups of patients, and the general adverse drug reactions were within the acceptable range. There are also some shortcomings in this study. PHN will have abnormal manifestations of inflammatory factors. This study did not study the correlation between the levels of inflammatory factors and the degree of pain with different medications.

In summary, duloxetine combined with pregabalin has good analgesic effect in the treatment of PHN, helps to improve the sleep quality of patients, and has high drug safety.

Conflict of interests:

The authors declared no conflict of interests.

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