

Observation of the Effect of Pregabalin Combined With Celecoxib in the Treatment of Acute Pain of Lumbar Intervertebral Disc Herniation

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Chen *et al.*: Combined Treatment of Pregabalin and Celecoxib in Lumbar Intervertebral Disc Herniation

This study involves the efficacy of pregabalin combined with celecoxib for acute pain treatment in patients with lumbar disc herniation. Selected 142 patients with acute pain due to lumbar disc herniation undertreated in our hospital from May 2019 to March 2021 and randomly divided them into a control group and a study group. Control group (n=71) accepted conventional treatment with celecoxib, after study group (n=71) accepted the same treatment as control group, they received another pregabalin, patients in both groups were treated continuously for 2 w. Visual analog scale scores of pain of both groups in 2, 7 and 14 d treatment were lower than those before treatment ($p<0.05$). Both groups had lower Oswestry disability index scores on the 7 and 14 d of treatment than before treatment ($p<0.05$) and Oswestry disability index scores of 14 d treatment were lower than those of 7 d treatment ($p<0.05$), but study group had lower Oswestry disability index scores in 7 and 14 d treatment than control group ($p<0.05$). Serum tumor necrosis factor alpha and interleukin-6 levels decreased after treatment in both groups ($p<0.05$), but study group possessed lower serum tumor necrosis factor alpha and interleukin-6 levels than control group ($p<0.05$). Both groups had no significant difference in adverse effects rate during the treatment period ($p>0.05$). Pregabalin combined with celecoxib can effectively relieve pain in patients with acute pain due to lumbar disc herniation, improve lumbar spine function, attenuate levels of inflammatory factors and has a good safety profile.

Key words: Pregabalin, celecoxib, lumbar disc herniation, acute pain

Lumbar Disc Herniation (LDH) refers to a neurogenic disease of lumbar disc degeneration, rupture of fibrous ring, outward protrusion of nucleus pulposus tissue and then compression of nerve root, resulting in waist and legs ache^[1]. Acute waist and legs ache easily happens in LDH patients, manifested as lumbosacral soreness, radiation pain in the lower limbs and sciatica. In severe cases, numbness occurs in the corresponding nerve distribution area, which has seriously influence on patient's daily life and work^[2]. Therefore, how to effectively reduce the acute pain of LDH patients is a problem that needs to be solved urgently in clinical practice. At present, drugs are commonly used clinically to relieve acute pain in LDH. Celecoxib is a non-steroidal anti-inflammatory analgesic. It inhibits the

biosynthesis of prostaglandins by inhibiting Cyclooxygenase-2 (COX-2), thereby offering effects of anti-inflammatory and analgesic^[3], but present study has indicated that the effect of celecoxib alone in the treatment of pain is often not ideal^[4]. Pregabalin is a receptor agonist that can regulate the central nervous system to control the influx of calcium ions, block the release of neurotransmitters and thereby control pain. It has been widely used in neuropathic pain treatment in recent years and has significant effects^[5]. Based on this, this study tried to apply pregabalin combined with celecoxib in the treatment of acute pain in LDH, to observe the therapeutic effect and it aimed to provide LDH patients a reference for acute pain treatment in clinic. Using random number table to select 142 patients

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with conservative treatment for LDH acute pain in our hospital from May 2019 to March 2021. 38 males and 33 females included in control group, ages were from 30 to 69 y old, average were about (47.62±6.45) y old, body mass index were 18.73-24.36 kg/m², average were about (22.13±1.05) kg/m², LDH course were from 3 to 18 mo, average were about (11.43±1.61) mo, acute pain time was from 6 h to 5 d, average were about (2.33±0.60) d; 36 males and 35 females included in study group, ages were from 28 to 66 y old, average were about (45.65±7.31) y old, body mass index were from 18.61 to 24.12 kg/m², average were (21.91±0.94) kg/m², LDH course were from 3 to 19 mo, average were (11.92±1.58) mo, acute pain time were from 6 h to 4 d, average were (2.28±0.57) d. Gender, age, body mass index, LDH course and acute pain time of both groups were not of significant difference ($p>0.05$). Inclusion criteria: All were diagnosed with LDH standard^[6]; all had typical acute pain manifestations; patients and their families signed informed consent. Exclusion criteria: Severe protrusion and compression of cauda equina nerve; requiring emergency surgical treatment; accompanied by other severe physical diseases; hepatic and renal insufficiency; nervous dysfunction; with a history of analgesic treatment in recent 1 mo; allergic to pregabalin or celecoxib and women during pregnancy and lactation. Treated control group with celecoxib and massage: Celecoxib capsules (Pfizer Pharmaceutical Co., Ltd., Guoyaozhunzi J20140072, 200 mg×6 capsules/box) orally, 0.2 g/time, 2 times/d; in addition, the patient's buttocks and lower back muscles are massaged with a relaxed technique, the position of the patient's spine was massaged up and down by reduction maneuver, massaged the patient's acupoints, 60 min/time, once a day, lasting 2 w. After receiving the same treatment as control group, study group received pregabalin capsules (Pfizer Pharmaceutical Co., Ltd., 75 mg×8 capsules/box, Guoyaozhunzi J20160021) orally, 1~10 d, 0.15 g/time, 3 times/d; the 10~14 d, 0.075 g/time, 3 times/d, lasting 2 w. Compare the pain conditions of both groups: Adopted Visual Analogue Scale (VAS)^[7] to evaluate the pain conditions of both groups before treatment and 2, 7 and 14 d after treatment, total 10 scores. Higher score means patient's pain more serious. Compare the lumbar spine function scores of both groups: Adopted Oswestry Dysfunction Index (ODI) score^[8] to evaluate the patient's lumbar spine function before treatment and 7 and 14 d after treatment, including 10 questions: Low back and leg pain, numbness of lower limbs, turning over from the supine position, posture transfer from

sitting to standing, walking, sitting, standing, sleeping, housework and work, 5 points for each question, total 50 points. Higher score means lumbar dysfunction more serious. Compare inflammatory factors levels of both groups: Before and after treatment, drew 5 ml of venous blood from both groups on an empty stomach, centrifuged at 3000 r/min for 10 min, collected the upper serum and adopted RT-6000 microplate reader (Beijing Perlong New Technology Co., Ltd.) to detect Tumor Necrosis Factor Alpha (TNF- α) and Interleukin-6 (IL-6) levels by enzyme-linked immunosorbent assay. Purchased the kits from Shanghai Yanzun Biological Technology Co., Ltd. Compare adverse reactions rate of both groups: Adverse reactions of celecoxib include dizziness, indigestion, abdominal pain, diarrhea, nausea and vomiting, etc.; adverse reactions of pregabalin include dizziness, somnolence, nausea and vomiting, and confusion. Adopted Statistical Package for the Social Sciences (SPSS) 25.0 software as a statistical tool. Used mean±standard deviation ($\bar{x}\pm s$) to indicate measurement data and tested by t. Compared the repeated measurement data by repeated measurement analysis of variance and tested by Least Significant Difference (LSD)-t. Expressed the count data by Percentage (%) and tested by χ^2 . $p<0.05$ was considered statistically significant. The difference of VAS score by repeated measurement analysis of variance possessed statistical significance ($p<0.05$); Both groups had lower VAS scores in 2, 7 and 14 d treatment than before treatment ($p<0.05$), VAS scores in 7 and 14 d treatment were lower than those in 2 d treatment ($p<0.05$) and VAS scores in 14 d treatment were lower than those in 7 d treatment ($p<0.05$), but study group had lower VAS scores in 2, 7 and 14 d treatment than control group ($p<0.05$), as shown in Table 1. The difference in ODI scores by repeated measurement analysis of variance possessed statistical significance ($p<0.05$). Both groups had lower ODI scores in 7 and 14 d treatment than before treatment ($p<0.05$) and ODI scores in 14 d treatment were lower than those in 7 d treatment ($p<0.05$), but study group had lower ODI scores in 7 and 14 d treatment than control group ($p<0.05$), as shown in Table 2. Both groups had no significant difference in TNF- α and IL-6 levels before treatment ($p>0.05$). After treatment, both groups had lower TNF- α and IL-6 levels than before treatment ($p<0.05$), but study group had lower TNF- α and IL-6 levels than control group ($p<0.05$), as shown in Table 3. The difference of adverse reactions rate in both groups had no statistical significance ($p>0.05$), as shown in Table

4. The number of patients with lumbar spondylosis in China is as high as 200 million and LDH accounts for about 15 % of the total number and it is showing an upward trend year by year^[9]. The lumbar intervertebral disc is an important structure of the human body. Lumbar disc hernia and the protrusion of the nucleus pulposus in patients with LDH lead to the compression of the patient's nerve roots, resulting in acute pain^[10]. Acute pain of LDH seriously affects the life, work and study of patients. Alleviating and eliminating pain is the urgent hope of patients with LDH^[11]. The mechanism of celecoxib is to prevent the production of prostaglandins by inhibiting the activity of COX-2, thereby inhibiting the secretion of inflammatory mediators, reducing the stimulation of inflammatory factors on nerve roots and then producing anti-inflammatory and analgesic effects^[12]. However, although celecoxib is easy to relieve pain, its efficacy is short and the effect of celecoxib alone is poor and does not essentially reduce the inducing factors of the disease, so the disease is easy to relapse^[13]. Therefore, it is necessary to increase analgesic drugs to relieve acute pain in patients with LDH. Our results showed that both groups had lower VAS scores of 2, 7 and 14 d treatment than before treatment, VAS scores of 7 and 14 d treatment were lower than those of 2 d treatment and VAS scores of 14 d treatment were lower than those of 7 d treatment, but study group had lower VAS scores in 2, 7 and 14 d treatment than control group; both groups had lower ODI scores in 7 and 14 d treatment than before treatment and ODI scores of 14 d treatment were lower than those of 7 d treatment, but study groups had lower ODI scores in 7 and 14 d treatment than control group, indicating that pregabalin combined with celecoxib could effectively alleviate the acute pain of patients with LDH and improve lumbar spine dysfunction. Li *et al.*^[14] and other studies reported that pregabalin combined with celecoxib could reduce postoperative pain in resting and active states of LDH patients and reduce the occurrence of preoperative and postoperative acute pathological neuropathic pain in patients with LDH, have better analgesic effect than celecoxib alone. The results of this study are consistent with it. Analysis of the reason: Pregabalin is one type of gamma aminobutyric acid analogue that interacts with voltage-gated calcium channels in central nervous system^[15] and inhibits the subunits $\alpha 2\delta$ ($\alpha 2\text{-}\delta$) protein of voltage-gated calcium channels in central nervous system through the blood-brain barrier, reduces the influx of calcium ions in nerve endings, inhibits the

release of excitatory neurotransmitters such as norepinephrine, glutamate, substance P and dopamine, and reduces the transmission of excitatory signals, so as to reduce central sensitization and pain threshold. The combination of pregabalin and celecoxib has a synergistic analgesic effect, which can quickly and effectively relieve pain and hyperalgesia symptoms^[16]. Our research found that after treatment both groups had lower inflammatory factors levels than before treatment, but study group had lower inflammatory factors levels than control group, indicating that pregabalin combined with celecoxib could more effectively reduce TNF- α and IL-6 levels of LDH patients. Research findings have proved that inflammatory factors levels such as TNF- α and IL-6 in the serum of LDH patients are higher than those of normal people and they have close relationship with patient's condition and the degree of low back and leg pain^[17]. Both TNF- α and IL-6 are cytokines that mediate inflammatory response and the increase of its level indicates the aggravation of local inflammatory response, which further aggravates the pain and other symptoms of LDH patients^[18]. As a non-steroidal anti-inflammatory drug, celecoxib blocks the cascade amplification effect of inflammatory mediators by inhibiting COX-2 and reduces the interaction between inflammatory mediators, so as to play a regulatory anti-inflammatory effect^[19]. The study by Xu *et al.*^[20] found that pregabalin could also inhibit the expression of COX-2 in the blood circulation by combining with $\alpha 2\text{-}\delta$ subunits and exert an anti-inflammatory effect. In addition, pregabalin can also inhibit the expression of docking protein 3, increase the anti-inflammatory effect of macrophages and inhibit the production of inflammatory factors TNF- α and IL-6^[21]. Therefore, the combined application of pregabalin and celecoxib can increase the anti-inflammatory pathway, improve the anti-inflammatory effect and significantly reduce the patient's serum inflammatory factor level. The results of this study showed that adverse reactions rate in study group was similar to control group, indicating that pregabalin will not increase the adverse reactions of patients and is safe. In summary, pregabalin combined with celecoxib can effectively relieve acute pain in patients with LDH, improve lumbar function, reduce the level of inflammatory molecules in the patient's body and has good safety. It is conducive to the treatment of patients with LDH, which is worthy to be popularized in clinic.

TABLE 1: COMPARISON OF PAIN ($\bar{x}\pm s$)

Grouping	n	Before treatment	On the 2 nd d of treatment	On the 7 th d of treatment	On the 14 th d of treatment
Study group	71	8.24±1.42	6.02±0.98 ^{ad}	4.02±0.64 ^{abd}	1.55±0.37 ^{abcd}
Control group	71	8.30±1.37	6.49±1.03 ^a	4.65±0.82 ^{ab}	2.77±0.52 ^{abc}
F		6.237 (between groups), 12.216 (time), 8.613 (interaction)			
p		0.012 (between groups), <0.001 (time), 0.001 (interaction)			

Note: Compared with before treatment, ^ap<0.05; compared with 2 d treatment, ^bp<0.05; compared with 7 d treatment, ^cp<0.05; compared with control group, ^dp<0.05

TABLE 2: COMPARISON OF LUMBAR FUNCTION SCORES ($\bar{x}\pm s$)

Grouping	n	Before treatment	On the 7 th d of treatment	On the 14 th d of treatment
Study group	71	43.51±5.26	30.39±4.17 ^{ac}	16.18±3.62 ^{abc}
Control group	71	42.85±5.89	33.72±4.34 ^a	23.59±3.78 ^{ab}
F		7.886 (between groups), 16.521 (time), 13.072 (interaction)		
p		0.005 (between groups), <0.001 (time), <0.001 (interaction)		

Note: Compared with before treatment, ^ap<0.05; compared with 7 d treatment, ^bp<0.05; compared with control group, ^cp<0.05

TABLE 3: COMPARISON OF INFLAMMATORY FACTORS LEVELS ($\bar{x}\pm s$)

Group	n	TNF- α (ng/l)		IL-6 (pg/ml)	
		Before treatment	After treatment	Before treatment	After treatment
Study group	71	15.31±3.68	5.48±1.72 ^a	156.76±20.24	68.82±6.03 ^a
Control group	71	15.29±3.71	8.35±2.34 ^a	154.11±21.08	94.65±12.65 ^a
t		0.032	8.327	0.764	15.531
p		0.974	<0.001	0.446	<0.001

Note: Compared with before treatment, ^ap<0.05; TNF- α : Tumor Necrosis Factor-alpha; IL-6: Interleukin-6

TABLE 4: COMPARISON OF ADVERSE REACTIONS (n %)

Group	n	Dizziness	Somnolence	Nausea and vomiting	Confusion	Indigestion	Abdominal pain and diarrhea	Total incidence
Study group	71	3 (4.23)	1 (1.41)	2 (2.82)	1 (1.41)	0 (0.00)	1 (1.41)	8 (11.27)
Control group	71	2 (2.82)	0 (0.00)	2 (2.82)	0 (0.00)	2 (2.82)	1 (1.41)	7 (9.86)
χ^2		0	0	0.257	0	0.507	0.507	0.075
p		1	1	0.612	1	0.476	0.476	0.785

Authors' contributions:

Jin Chen and Yun Xiang have contributed equally to this work.

Conflict of interests:

The authors declared no conflicts of interest.

REFERENCES

1. Zhao J, Zhao CY. Effect of integrated Chinese and Western medicine therapy on pain and analgesia in acute stage of lumbar intervertebral disc herniation. *Chin J Surg Integr Tradit West Med* 2020;26(4):625-9.
2. Spinal pain group of pain credit association of Chinese Medical Association. Consensus of Chinese pain experts on the diagnosis and treatment of lumbar disc herniation. *Chin J Pain Med* 2020;26(1):2-6.
3. Wu RD, Bai YH, Ni YM. Clinical study of Honghua injection combined with celecoxib in treatment of lumbar disc herniation. *Drug Eval Res* 2020;43(9):1831-5.
4. Zhu YC, Wang ZP. Dexamethasone combined with celecoxib in the treatment of knee osteoarthritis. *Orthop J China* 2021;29(1):82-4.
5. Zheng JL, Luo X, Guo L. Clinical comparison of pregabalin and oxcarbazepine in the treatment of neuropathic pain. *Chin J Integr Med Cardiovasc Dis* 2021;19(20):3613-6.
6. Xu ST, Ge BF, Xu YK. Practical orthopedics. 3rd ed. Beijing: People's Military Medical Press; 2006. p. 1337.

7. Sun B, Che XM. Visual analogue scale (VAS). *Chin J Neurosurg* 2012;28(6):645.
8. Cheng J, Wang Z, Liu W, Xing Y, Li C, Li C, *et al.* Improvement of Oswestry disability index and its test of reliability and validity. *Chin Spine Spinal Cord* 2017;27(3):235-41.
9. Zhao L, Ma Q, Zhang YL. Effects of medicine separated moxibustion combined with pressing beans at ear points on pain and sleep quality in patients with lumbar disc herniation. *Mod J Integr Tradit Chin West Med* 2021;30(4):420-6.
10. Benzakour T, Igoumenou V, Mavrogenis AF, Benzakour A. Current concepts for lumbar disc herniation. *Int Orthop* 2019;43(4):841-51.
11. Costa T, Linhares D, da Silva MR, Neves N. Ozone therapy for low back pain: A systematic review. *Acta Reumatol Port* 2018;43(3):172-81.
12. Hu CP, Mou CL, Liu QZ. Clinical study of Zhanjin huoxue decoction combined with celecoxib in the treatment of residual pain after foraminal endoscopy for lumbar disc herniation. *J Hebei Tradit Chin Med Pharmacol* 2020;35(6):24-6.
13. García-Rayado G, Navarro M, Lanás A. NSAID induced gastrointestinal damage and designing GI-sparing NSAIDs. *Expert Rev Clin Pharmacol* 2018;11(10):1031-43.
14. Li Z, Zeng J, Nie H, Jiang H, Xie T, Song Y. Effectiveness of combined pregabalin and celecoxib for treatment of neuropathic pain after percutaneous endoscopic lumbar discectomy. *Chin J Reparative Reconstr Surg* 2017;31(2):215-21.
15. Bidari A, Moazen-Zadeh E, Ghavidel-Parsa B, Rahmani S, Hosseini S, Hassankhani A. Comparing duloxetine and pregabalin for treatment of pain and depression in women with fibromyalgia: An open-label randomized clinical trial. *DARU J Pharm Sci* 2019;27(1):149-58.
16. Routray SS, Pani N, Mishra D, Nayak S. Comparison of pregabalin with gabapentin as preemptive analgesic in lumbar spine surgery. *J Anaesthesiol Clin Pharmacol* 2018;34(2):232-6.
17. Li HT, Wei XR, Sun XW. Effect of Jitongxiao capsule on levels of serum IL-1 β , IL-6 and TNF- α in the treatment of LDH. *Inform Tradit Chin Med* 2020;37(2):95-9.
18. Andrade P, Cornips EMJ, Sommer C, Daemen MA, Visser-Vandewalle V, Hoogland G. Elevated inflammatory cytokine expression in CSF from patients with symptomatic thoracic disc herniation correlates with increased pain scores. *Spine J* 2018;18(12):2316-22.
19. Bi HH, Zhang X. The curative effect of intrathecal injection of pregabalin on postherpetic neuralgia in rats and its effect on the expression of COX2 in spinal cord. *Guangdong Med J* 2019;40(2):163-7.
20. Xu LE, Zhao JJ, Du Y. Effect of celecoxib on behavior and central inflammatory in rats with pain accompanied by depression. *J Clin Exp Med* 2021;20(1):1-4.
21. Gao WS, Qu YJ, Huai J, Wei H, Zhang Y, Yue SW. DOK3 is involved in microglial cell activation in neuropathic pain by interacting with GPR84. *Aging* 2021;13(1):389-410.

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