Pregabalin Versus Acetaminophen for a Treatment of Chronic Neuropathic Pain on Extremities after Cervical Surgery: A Prospective Randomized, Open-Label Preliminary Study

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Abstract

Therapeutic efficacy of pregabalin (PGL) for reducing neuropathic pain in patients who received a cervical operation is unclear. The purpose of this prospective pilot study was to compare the efficacy and adverse events between PGL and acetaminophen (ACM) for residual neuropathic pain. Thirty-four patients who received cervical spine surgery at our hospital from September 2011 to April 2013 and were diagnosed with residual neuropathic pain in the extremities were enrolled and were randomized to receive PGL (50 mg/day initially as an induction dose for 2 weeks) or ACM (1200 mg/day) for 8 weeks. PGL dosage was adjusted to 50-150 mg/day according to the severity of pain using a visual analog scale (VAS) after a 2-week time point. The Neck Disability Index (NDI) and VAS were used to evaluate subjective pain of the extremities and sleep condition. Short Form-36 (SF-36) and Japanese Orthopedic Association Cervical Myelopathy Evaluation Questionnaire (JOACMEQ) were used to evaluate neurologic function. Thirty-three patients (PGL 19 cases, ACM 14 cases) completed 8 weeks of follow-up. The average VAS for pain and numbness significantly improved in both groups at the final visit. The scale for sleep improved in the PGL group but was unchanged in the ACM group. The proportion of patients with satisfactory

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(3) pain on the upper and/or lower extremities that are caused by a reason other than a spinal disorder; (4) significant motor deficits and/or bowel or bladder dysfunction; and (5) history of another spinal operation.

Among 168 patients who received cervical spine surgery at our hospital from September 2011 to April 2013, 34 consecutive patients (26 men, 8 women) who were newly diagnosed with chronic neuropathic pain following cervical spine surgery were enrolled (Figure 1). These patients were randomized into two groups using a random number table. In the pregabalin (PGL) group, patients started pregabalin (Lyrica®) at a dose of 50 mg/day as an induction dose for 2 weeks. Patients with visual analog scale (VAS) of less than 40 mm at the 2-week time point maintained the initial dose for 2 more weeks. If the dose did not produce sufficient pain relief, with a VAS of greater than or equal to 40 mm, it was increased to 100 mg/day for 2 weeks. Patients received the agent at a dose up to 150 mg/day during the follow-up period if VAS was greater than or equal to 40 at the 4-week time point. The total treatment period was 8 weeks. In the acetaminophen (ACM) group, patients received acetaminophen (Calonal®) 1200 mg/day for 8 weeks.

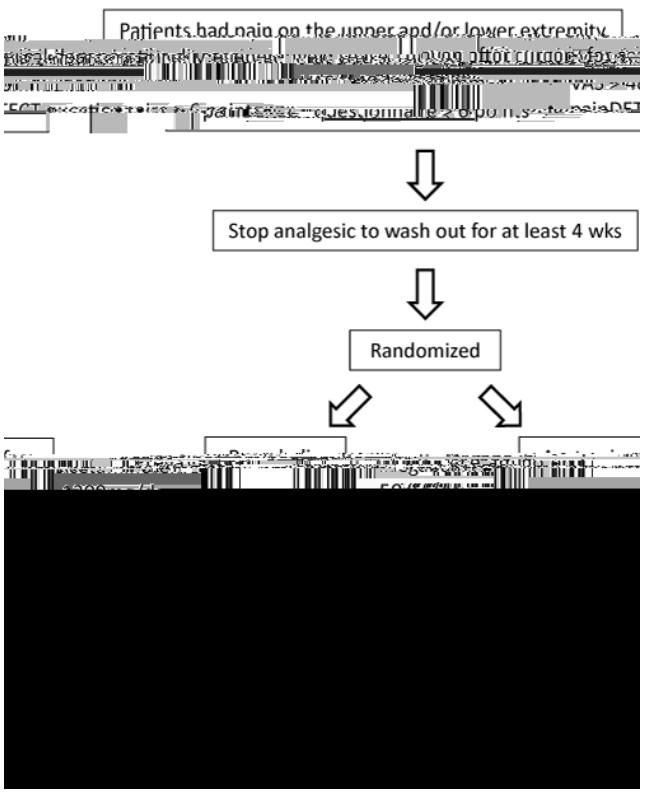

Figure 1: Flowchart of dosages in the pregabalin and acetaminophen groups.

The Neck Disability Index (NDI) and VAS were used to evaluate the severity of subjective pain of the upper and/or lower extremities and condition of sleep. Subjective sleep quality was rated from 0 mm ('Best night of sleep ever') to 100 mm ('worse night of sleep ever'). Short Form-36 (SF-36) and Japanese Orthopedic Association Cervical Myelopathy Evaluation Questionnaire (JOACMEQ) were used to

	Bladder	70.8 Ñ 26.2/74.0 Ñ 24.7	79.6 Ñ 17.6/85 Ñ 13.6
	Quality of life	47.7 Ñ 24.0/50.1 Ñ 22.9	55.5 Ñ 13.1/56.8 Ñ 10.9

Values represent mean Ñ standard deviation. PGL, pregabalin; ACM, acetaminophen; CSM, cervical spondylotic myelopathy; OPLL, ossification of the posterior longitudinal ligament; CDH, cervical disc herniation; ADF, anterior decompression with fusion; LAMP, laminoplasty; JOA, Japanese Orthopedic Association; VAS visual analog scale; JOACMEQ, Japanese Orthopedic Association Cervical Myelopathy Evaluation Questionnaire

incidence of these adverse events showed no significant differences between the PGL and ACM groups (Table 3), the number of patients who complained of somnolence tended to be greater in the PGL group.

	PGL group	ACM group	P
	(n=19)	(n=14)	
Somnolence	3	0	0.11
Dizziness	2	1	0.74
Nausea	1	0	0.38
Peripheral edema	1	0	0.38
Weight gain	1	0	0.38
PGL: pregabalin; ACM: acetaminophen			

Table 3: Summary of common treatment-emergent adverse events

Discussion

The results of the present study can be summarized as follows: (1) both pregabalin and ACM administration improved residual neuropathic pain in patients treated with cervical spine surgery for myelopathy; (2) pregabalin was effective for reducing sleep interference related to refractory neuropathic pain compared with ACM; (3) pregabalin sometimes brought about adverse effects such as somnolence, dizziness, and peripheral edema. These results are consistent with the evidence that pregabalin is an effective treatment for chronic neuropathic pain caused by a disease of the central nervous system including post-stroke, spinal cord injury, and multiple sclerosis. However, residual neuropathic pain in patients treated with cervical decompression surgery, on which the present study focused, could be considered as a pain state that is more complicated than diseases investigated by other studies. The pathology consists of two distinct mechanisms: one is neuronal damage in the central nervous system caused by compression, and the other is residual abnormality in the peripheral nervous system. In patients who had suffered from neuropathic pain caused by myelopathy for a long time, these two pain states might be irreversible even after cervical decompression operation and often distress patients.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was introduced in 2000 to assess the quality of evidence and gained widespread international acceptance. To date, various randomized trials for treatment of refractory neuropathic pain have been performed and several drugs have been identified as effective medication based mainly on the GRADE recommendations. Tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitor antidepressants, pregabalin, gabapentin, and gabapentin extended release or enacarbil have strong GRADE recommendations for use in neuropathic pain and are proposed as first-line treatments. Notably, earlier studies of gabapentinoid [11] as a treatment for chronic neuropathic pain had demonstrated that pregabalin and gabapentin decreased mean daily pain intensity with an acceptable safety profile, and had calculated the number needed to treat (NNT) for 50% pain intensity reduction. A meta-analysis concluded that the overall NNT was 7.7 (95% CI, 6.5–9.4) for pregabalin and 6.3 (95% CI, 5.0–8.3) for gabapentin, and these drugs provide good outcomes not only for peripheral neuropathic pain but also central neuropathic pain.

This study revealed that not only PGL but also ACM improved residual refractory pain in patients treated with cervical decompression surgery. Although it has been reported that ACM does not affect neuropathic pain mechanisms [12], there are reports of positive effects of ACM for neuropathic pain. ACM attenuates hypersensitivities caused by neuropathic pain such as chemotherapy-induced pain [13] and partial sciatic nerve ligation models [14]. Several preclinical studies suggested the mechanisms of analgesic action of ACM. One is an increase of serotonin levels released from the brainstem serotonergic neurons in the central nervous system. Another is action either directly