Additive Effect of Pregabalin/Tramadol Combination in the Treatment of the Neuropathic Pain
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Purpose
Neuropathic pain which accompanies moderate to severe unremitting chronic pain caused by a primary lesion or dysfunction in the nervous system has been described as 'the most terrible of all tortures'. However, because there is currently no proven treatment to prevent or cure neuropathic pain, the primary goals of neuropathic pain treatment are to reduce the pain as much as possible. Pregabalin, a calcium channel α2-δ ligand, is the only treatment receiving an A grade from the American Academy of Neurology among a variety of first-line treatments, indicating that its effectiveness had been firmly established in clinical trials. However, only approximately 35% of the pregabalin treated patients had a 50% improvement. Therefore, tramadol, a weak μ-opioid analgesic, has been often prescribed in combination with pregabalin in the clinical situation when patients do not have a satisfactory response to the pregabalin alone. To overcome the insufficient pain relief and improve the patient's convenience, we developed a new combination drug of pregabalin and tramadol which was physicochemically stable at the accelerated storage condition for 6 month and investigated whether the combination drug is more effective than pregabalin alone in a neuropathic pain animal model.

Methods
The Bennett and Xie chronic constriction injury model, one of the most widely used chronic neuropathic pain animal models was used. The sciatic nerve of male Sprague-Dawley rats was loosely tied with four ligatures around the nerve with 1 mm spacing. Rats with paw withdrawal threshold (PWT) below 3.6 g were selected using a series of calibrated von Frey filaments (range 0.4-15 g) and then orally administered with vehicle, pregabalin (6 mg/kg, 12 mg/kg), and combination of pregabalin and tramadol (6/4 mg/kg, 12/8 mg/kg). The combination ratio of pregabalin and tramadol was determined considering the maximum recommended human dose of pregabalin and tramadol, respectively. The PWT was measured 1 h and 2 h after drug treatment.

Results
A significant increase in PWT was observed at 1 h (p<0.05) and 2 h (p<0.05) after administration of 6 mg/kg pregabalin with 4 mg/kg tramadol (8.72 ± 5.71 g, 10.12 ± 5.44 g) compared to vehicle (2.43 ± 1.11 g, 1.96 ± 1.12 g) and 6 mg/kg pregabalin alone (4.23 ± 2.70 g, 6.05 ± 3.72 g), respectively. The PWT at 2 h (p<0.01) after administration of 12 mg/kg pregabalin with 8 mg/kg tramadol (12.86 ± 3.87 g) was significantly increased compared to vehicle (2.98 ± 0.46 g) and 12 mg/kg pregabalin (8.68 ± 3.77 g), reaching approximately 90% PWT of the sham group (14.30 ± 1.66 g). All treatment groups showed higher efficacy at 2 h than 1 h after drug treatment.

Conclusion
Our study shows that pregabalin/tramadol combination is significantly more efficacious than pregabalin alone in a neuropathic pain animal model. Now, we are conducting phase I clinical trial. If their additive effect is confirmed by phase II/III clinical trials planned for next year, pregabalin/tramadol combination drug can be very helpful to neuropathic pain patients.