Intravenous Nefopam Reduces Postherpetic Neuralgia during the Titration of Oral Medications

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Background:
The recently known analgesic action mechanisms of nefopam (NFP) are similar to those of anticonvulsants and antidepressants in neuropathic pain treatment. It is difficult to prescribe high doses of oral neuropathic drugs without titration due to adverse effects. Unfortunately, there are few available intravenous analgesics for the immediate management of acute flare-ups of the chronic neuropathic pain. The aim of this study was to determine the additional analgesic effects for neuropathic pain of NFP and its adverse effects during the titration of oral medications for neuropathic pain among inpatients with postherpetic neuralgia (PHN).

Methods:
Eighty inpatients with PHN were randomly divided into either the NFP or normal saline (NS) groups. Each patient received a 3-day intravenous continuous infusion of either NFP with a consecutive dose reduction of 60, 40, and 20 mg/d, or NS simultaneously while dose titrations of oral medications for neuropathic pain gradually increased every 3 days. The efficacy of additional NFP was evaluated by using the neuropathic pain symptom inventory (NPSI) score for 12 days. Adverse effects were also recorded.

Results:
The median NPSI score was significantly lower in the NFP group from days 1 to 6 of hospitalization. The representative alleviating symptoms of pain after using NFP were both spontaneous and evoked neuropathic pain. Reported common adverse effects were nausea, dizziness, and somnolence, in order of frequency.

Conclusions:
An intravenous continuous infusion of NFP reduces spontaneous and evoked neuropathic pain with tolerable adverse effects during the titration of oral medications in inpatients with PHN. (Korean J Pain 2014; 27: 54-62)

Key Words:
anticonvulsants, antidepressants, nefopam, postherpetic neuralgia, titration.
INTRODUCTION

Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system” [1]. In cases of a new patient with acute flare-ups or exacerbation of neuropathic pain, there are few available intravenous medications for neuropathic pain so far. A neural blockage may be an answer until dose titrations of oral medications for neuropathic pain reach beyond the pain threshold. A continuous neural blockage or neural ablation after hospitalization is the next procedure for a new patient who has already received a neural blockage and is referred from another pain clinic. However, titration of oral medications for neuropathic pain for preparing the patient’s discharge is also needed even after a continuous neural blockage or neural ablation. It is difficult to prescribe high doses of oral neuropathic drugs from the beginning without titration due to their common adverse effects, therefore, it takes at least three days to raise and maintain the concentration of drugs beyond the pain threshold.

Nefopam (NFP) is a non-opioid clinically potent analgesic, whose mechanism of action is not fully understood. The known analgesic action mechanisms of NFP are the inhibitions of the synaptosomal uptakes of serotonin, norepinephrine and dopamine, known as serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI), or triple reuptake inhibitor (TRI) [2]. NFP’s mode of action is similar to that of antidepressants in the treatment of neuropathic pain. In addition, it also inhibits calcium influx, cGMP formation, and NMDA receptor-dependent neurotoxicity following activation of voltage sensitive calcium channels [3]. In contrast, in some reports, nefopam blocks voltage-sensitive sodium channels and modulates glutamatergic transmission [4-8]. However, there have been few compelling human studies of NFP in the management of neuropathic pain related to its descending inhibition of pain [9]. Most studies related to NFP have focused on analgesic effects for nociceptive pain related to acute postoperative pain and a comparison of its analgesic potency with morphine [10,11]. Several recent studies have been refocused on the prevention of postoperative shivering [12,13].

The aim of this study was to determine the additional analgesic effects for neuropathic pain using continuous intravenous infusion of NFP, as well as its adverse effects during the titration of oral neuropathic medications among inpatients with postherpetic neuralgia (PHN) based on the analgesic action mechanisms of NFP.

MATERIALS AND METHODS

1. Participants

After Institutional Review Board approval was obtained, 80 inpatients with intractable PHN and in need of titration of oral medications for neuropathic pain were enrolled into this prospective, randomized, double blinded study.

2. Inclusion criteria

The enrollment took place from January 2011 through December 2012 in a pain clinic of a university hospital. Inclusion criteria were the inpatients with PHN with an initial neuropathic pain symptom inventory (NPSI) [14] over 70%, aged between 20 and 80 years, and estimated glomerular filtration rate over 60 mg/dl. PHN was defined as pain persisting beyond 120 days from rash onset [15].

3. Exclusion criteria

Exclusion criteria included patients with contraindications of NFP administration, such as a history of epilepsy, myocardial infarction, convulsion, risk of urinary retention due to urethra or prostate problems, closed angle glaucoma, monoamine oxidase inhibitors administrator, and pregnancy or breast feeding. The patients with previous oral administration for PHN over the dose of pregabalin 150 mg, nortriptyline 25 mg, and tramadol 100 mg per day were also excluded in this study. Other excluded patients were those who could not understand or fill in the NPSI score.

4. Randomization-sequence generation and randomization-allocation concealment

Using a computer–generated random allocations sequence, 80 patients with PHN were randomized and assigned into 2 equal groups: a NFP group and a normal saline (NS) group.

5. Blinding (masking)

The doses of oral medications for PHN, which escalated every 3 days, were decided by the same investigator and all follow-ups were performed by another investigator. Both the participants and the care providers did not know whether intravenous drugs contained NFP or not.