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Do Interventional Pain Management Procedures during the Acute Phase of Herpes Zoster Prevent Postherpetic Neuralgia in the Elderly?: A Meta-Analysis of Randomized Controlled Trials

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Dear Editor:

Postherpetic neuralgia (PHN) is clinically significant pain presenting 30～180 days after the onset of the skin rash of herpes zoster (HZ)[1-5]. The reported risk of developing PHN varied from 5% to >30%, depending on the study design, age distribution of the study population, and definition. More than 30% of patients with PHN experienced persistent pain for >1 year[6]. In elderly patients, the prevention of PHN has major implications on the patients' daily activity and quality of life.

Antiviral agents used at the time of the rash and active interventional pain management procedures (IPs) for early pain control have been proposed as methods to prevent the development of PHN[3,7]. A recent meta-analysis showed high-quality evidence that oral acyclovir does not reduce the incidence of PHN significantly. In addition, this study demonstrated insufficient evidence to determine the effect of other antiviral treatments such as famciclovir[7]. Although several IPs, such as epidural sympathetic block to reduce the acute HZ-related pain, have been indicated to have some level of effectiveness in the prevention of PHN, there is no conclusive evidence at present. Dermatologists are the ideal sentinels for the early management of HZ and the prevention of PHN. Therefore, dermatologists should be aware of the effects of early IPs in the prevention of PHN.

The aim of this study was to evaluate the evidences about the efficacy of IPs during the acute phase of HZ (within 14 days after the onset of the rash) on the prevention of PHN in elderly patients, through a systematic review with a meta-analysis of randomized controlled trials (RCTs).

The databases that we used included PubMed, SCOPUS, and the references of retrieved articles from inception to August 31, 2013. In this study, combinations of the following keywords were used for the literature search: "analgesia", "electrical nerve stimulation", "epidural", "herpes zoster", "herpes zoster-related pain", "injection", "intervention", "interventional pain management", "nerve block", "pain", "paravertebral", "postherpetic neuralgia", "shingles related pain", and "sympathetic", with no limits on the study date or language. We focused on RCTs that analyzed the association between the IPs during the acute phase of HZ and PHN occurrence. The studied population consisted of elderly patients (≥50 years old) with the acute phase of HZ. The evaluated intervention was various types of IPs. The outcome was PHN development (≥ 3 months) in the elderly. All of the selected studies must have included the use of a visual analogue scale (VAS) for pain assessment. Two evaluators independently evaluated all the reports retrieved from the databases. We estimated the pooled odds ratios (ORs) and 95% confidence inter-

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vals (CIs) by using Comprehensive Meta Analysis (version 2.0; Biostat Inc., Englewood, NJ, USA). As shown in Fig. 1, 2,670 articles were obtained after the initial search of the databases and relevant bibliographies. After excluding 710 duplicate articles and 1,935 articles that did not meet the selection criteria, we reviewed the full text of the 25 articles. Among these, only five RCTs were included in the final analysis[1-5].

The final analysis from five RCTs included 1,405 total subjects, 708 of whom received IPs with or without standard antiviral medication such as acyclovir or famciclovir and 697 received standard antiviral therapy only. The types of IPs were as follows: epidural and paravertebral block, stellate ganglion block, and percutaneous electrical nerve stimulation (Table 1). The funnel plot of this meta-analysis showed asymmetry; however, the distribution was regular. Therefore, we analyzed the data by using a random-effects model. The results of meta-analysis showed that IPs with or without antiviral therapy during acute HZ had a preventive effect on the development of PHN over antiviral therapy at 3 months (OR 3.28, 95% CI 1.20～8.96; p=0.02) and 6 months (OR 3.86, 95% CI 1.25～11.89; p=0.02) (Fig. 2). Further subgroup analyses according to the type of prevention and sexual differences showed no effect on the prevention of PHN.

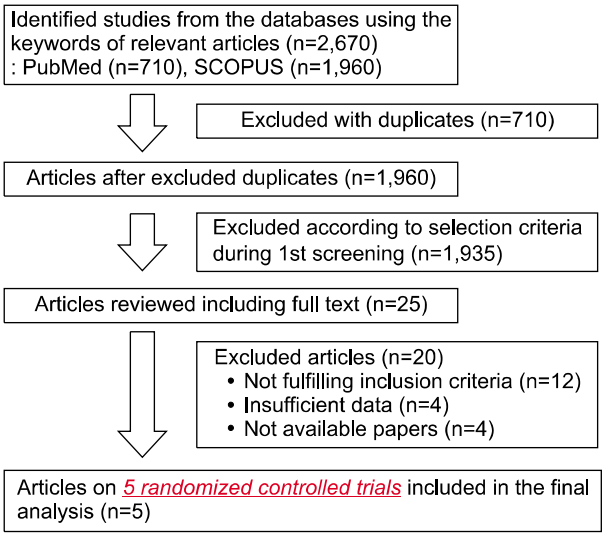

Fig. 1. Evaluation diagram of articles found in the literature.

The mechanism of PHN remains unclear; however, ganglionitis and neuritis of the affected nerve result in sympathetic stimulation, which leads to decreased intraneural blood flow, resulting in nerve ischemia and finally in irreversible nerve damage[8]. Early IPs that reduce repetitive painful stimuli and prevent vasoconstriction during the acute phase of HZ may attenuate central sensitization, prevent nerve scarring, and substantially account for the prevention of PHN.

This study has some limitations. Funnel plot analysis, the value of which was limited by the small number of stud-

Table 1. Characteristics of the five RCTs included in the final analysis

Article	No. of patient	Age of patient (yr)	Duration of skin rash (day)	Definition of PHN	Control vs. IP group	
					Control	IP group
Ahmed et al., 1998[1]	50	All ages	<3	The presence of pain in a dermatomal pattern after 3 months (VAS≥1)	Standard	Percutaneous electrical nerve stimulation
Pasqualucci et al., 2000[2]	569	≥55	<7	Pain or abnormal sensation after 1 month (VAS≥1)	Standard	Epidural block (bupivacaine, methylprednisolone acetate)
van Wijck et al., 2006[3]	590	≥50	<7	Pain (VAS≥1)	Standard	Standard plus epidural block (bupivacaine, methylprednisolone acetate)
Ji et al., 2009[4]	132	≥50	≤7	Burning and lancinating pain that was accompanied by allodynia after 3 months (VAS≥1)	Standard	Standard plus paravertebral block (bupivacaine, methylprednisolone acetate)
Makharita et al., 2012[5]	64	≥50	<14	Persistent herpetic pain after 3 months (VAS≥1)	Standard*	Standard plus stellate ganglion block (bupivacaine, dexamethasone)
Total	1,405					

RCT: randomized controlled trial, PHN: postherpetic neuralgia, IP: interventional pain management procedure, VAS: visual analogue scale. *Oral antiviral therapy such as acyclovir or famciclovir.

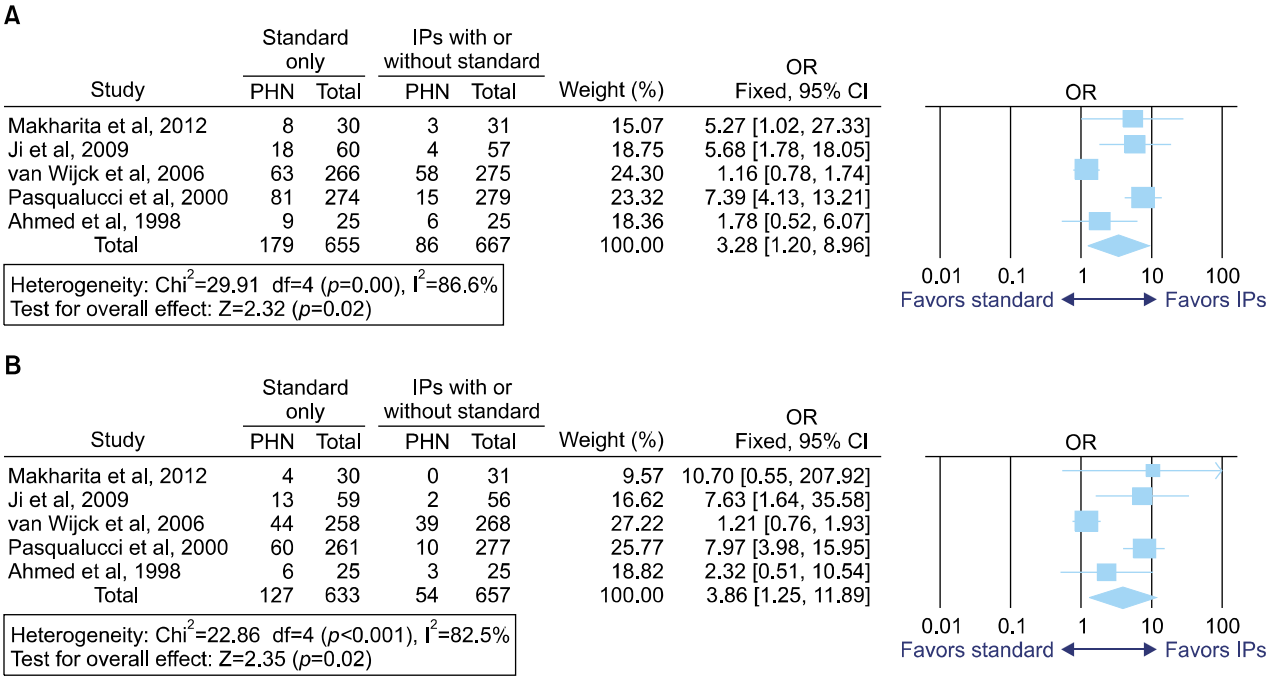

Fig. 2. Results of the meta-analysis of five randomized controlled trials. The efficacy of interventional pain management procedures with or without antiviral therapy during acute herpes zoster had significant preventive effects on the development of postherpetic neuralgia over antiviral therapy at 3 months (A; odds ratio [OR] 3.28, 95% confidence interval [95% CI] 1.20～8.96; p=0.02) and 6 months (B; OR 3.86, 95% CI 1.25～11.89; p=0.02). PHN: postherpetic neuralgia, IPs: interventional pain management procedures.

ies, showed a slight asymmetry that could be due to publication bias. This means that smaller studies showing low effects on the prevention of PHN could have not been published. In addition, we pooled studies in which PHN was treated by using different IPs, such as epidural and paravertebral block, stellate ganglion block, and percutaneous electrical nerve stimulation. This could be viewed as a source of heterogeneity. These factors could have led to some overestimation of IPs.

Although the sample size is relatively small to be conclusive, the present meta-analysis showed that by preventing PHN, IPs can be effective during acute HZ in elderly patients. However, more data from RCTs will be needed to confirm these results. In the treatment of HZ, dermatologists have a tendency to hesitate about providing early, active management of HZ-related pain. Active management of acute HZ-related pain through an early multidisciplinary approach with pain management specialists may be helpful in preventing PHN development.

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The Clinical Efficacy of Azathioprine in Korean Patients with Atopic Dermatitis

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Dear Editor:

Atopic dermatitis (AD) is a chronic, distressing disease often requiring systemic treatment for disease control[1]. Drug candidates for AD, however, are limited; the long-term use of systemic steroid raises concerns for metabolic adverse effects, and cyclosporine has potential nephrotoxicity and is contraindicated in uncontrolled hypertensive patients. Azathioprine, an imidazole derivative of 6-mercaptopurine, is one of the alternative choices in the treatment of recalcitrant AD. Yet, its efficacy in AD patients has not been thoroughly investigated in Asian population.

From a computerized institutional database, we identified AD patients who underwent treatment with azathioprine from December 2009 to January 2011. A total of 20 patients were included (16 men, 4 women; mean age, 28.65±9.51 years; range, 13~43 years). Azathioprine was started at a dose of 100 mg/day. All patients were allowed to take antihistamine and topical steroids for symptomatic control and the management of localized lesions. The mean duration of azathioprine treatment was 22.20±19.85 weeks.

Overall, compared with baseline, improvements were observed in the eczema area and severity index (EASI) score from 26.12±3.20 to 15.15±3.05 ($p<0.017$) (Fig. 1). On the visual analogue scale, the degree of pruritus decreased from 7.35±1.66 to 4.10±2.89 ($p<0.001$) along with a

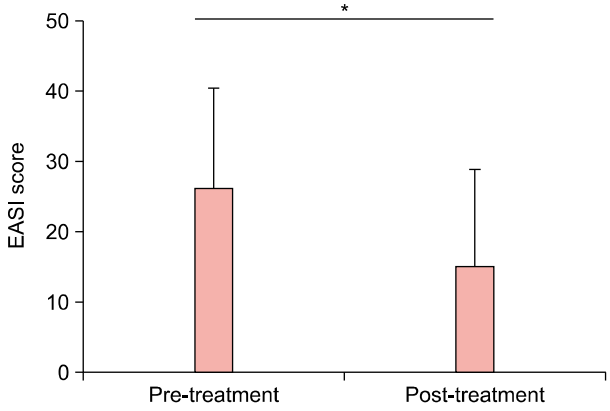

Fig. 1. Change in the eczema area and severity index (EASI) score before and after azathioprine treatment (mean treatment duration, 22.20±19.84 weeks). There was a 42% reduction in the EASI score from the baseline ($p<0.017$). *Statistically significant difference compared with the baseline.

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