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A Single-Center Randomized Controlled Trial of Local Methylcobalamin Injection for Subacute Herpetic Neuralgia

Gang Xu, MD, Zhong-Wei Lv, PhD, Yan Feng, BSc, Wei-Zhen Tang, BSc, and Gang (Xiao) Xu, BSc

Department of Rehabilitation Medicine, Affiliated Tenth People's Hospital of Tongji University, Shanghai, China

Reprint requests to: Gang Xu, MD, Department of Rehabilitation Medicine, Affiliated Tenth People's Hospital of Tongji University, 301 Middle Yanchang Road, Shanghai 200072, China. Tel: +86-21-66306496; Fax: +86-21-64940427; E-mail: shiter@yeah.net.

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Abstract

Objective. This study explored the efficacy of local methylcobalamin injection in relieving pain and improving the quality of life among subjects with subacute herpetic neuralgia.

Design. A single-center, randomized controlled trial of local methylcobalamin injection was performed.

Subjects. Ninety-eight subjects (age, ≥50 years) with unilateral, dermatomal pain ≥4 related to herpes zoster on the torso lasting for 30 days after onset of rash were enrolled.

Methods. Subjects were randomized to receive local methylcobalamin injection (N = 33), oral methylcobalamin (N = 33), or subcutaneous 1.0% lidocaine injection (N = 32) for 4 weeks. Worst pain severity, global impression of change, continuous spontaneous pain, paroxysmal pain, allodynia, paresthesia, interference with activities of daily living, and quality of life were assessed after 28-day treatment period.

Results. Time per group interaction and group difference on overall pain at each follow-up point were statistically significant ($P < 0.001$) among groups. In the injected methylcobalamin group, the overall pain ($P < 0.001$), continuous spontaneous pain ($P < 0.05$), paroxysmal pain ($P < 0.05$), and allodynia ($P < 0.05$) revealed a significant effect at each follow-up point as compared with the other groups. Twenty subjects achieved pain reduction ≥50%, 24 perceived worst pain ≤3, 24 stopped using analgesics at end point; activities of daily living and quality of life improved significantly as compared with the other groups ($P < 0.001$). Although both of the other groups showed a significant response after the 14-day treatment ($P < 0.001$) compared with the baseline, oral methylcobalamin did not provide any significantly pain relief ($P > 0.05$).

Conclusions. Local methylcobalamin injection was not only efficacious in relieving pain, but also appears to be tolerable and a potential choice of treatment for subacute herpetic neuralgia.

Key Words. Subacute Herpetic Neuralgia; Cobalamin; Subcutaneous Injection; Randomized Clinical Trial

Introduction

Varicella zoster virus (VZV) is a neurotropic virus and latent in trigeminal, autonomic, and dorsal root ganglia [1,2]. Although varicella vesicles can develop in any dermatome, shingles (zoster) and mononeuritis are characterized by axonal damage and myelin disruption [3], resulting in zoster-associated pain that often remains confined to a single dermatome even if there may be cutaneous spread beyond the originally affected dermatome [2,4,5]. Subacute herpetic neuralgia (SHN) is defined as pain beyond the acute phase that persists for approximately 30 to 120 days after the onset of vesicles [6,7]. Patients with SHN who are at least 50 years old are more likely to have severe pain and easily develop postherpetic neuralgia (PHN) [8]. Existing interventions, such as systemic agents or localized therapies, do not completely cure all cases of PHN [9,10]. The outcome of aggressive and effective treatment for SHN in the early stage is much better than that of the treatment of PHN, which is an urgent public health problem. The persistence of pain after the onset of vesicles implies that the damaged neural tissues, such as afferent fibers, subepidermal nerve plexus, epidermal

nerve fiber and endings [11–13], play an important role in the pathogenesis of SHN and PHN [14]. We speculate that some strategies, such as neurotrophic medication that promote the repair or regeneration of damaged fibers, might be potentially relevant, and local administration of high concentrations of neurotrophic drug may have more significant neurotrophic effect than its systemic administration on affected fibers and epidermal nerve endings.

Cobalamin (Cbl) is a neurotrophic agent that has a special affinity for neural tissues. It promotes myelination and transport of the axonal cytoskeleton, can help maintain the nervous system, and regenerates peripheral nerves [15,16]. Tissue distribution, intracellular localization of Cbl and its dynamics in the peripheral nervous system differ from those in the central nervous system [17]. High-dose Cbl therapy may have salutary pharmacological effects on neurological function in various disorders [18]. Recent studies have suggested that oral administration of Cbl is better than parenteral supplementation [19]. However, to achieve the same effectiveness as that of the intramuscular administration in obtaining short-term neurological responses in subjects with Cbl deficiency, long-term and high doses of daily oral Cbl is required [20]. Clinical experience has shown that Cbl therapy improves symptoms of both peripheral neuropathy and autonomic dysfunction [21], while intrathecal high-dose methylcobalamin (MeB_{12}) can relieve symptoms of neuropathy [22]. As delayed therapy can lead to irreversible neurological dysfunction, parenteral Cbl therapy should be strongly considered [18,23]. Based on the neurotrophic effects of Cbl [15,16], we focused our research on therapeutic effects of local Cbl administration on SHN in a single-center, randomized controlled study at Affiliated Tenth People's Hospital of Tongji University, Shanghai, China, during the period from September 2011 to April 2012. All procedures were conducted in accordance with the Good Clinical Practice Guidelines as well as the Declaration of Helsinki. Necessary approvals were obtained from the Tongji University Institutional Review Board. All eligible subjects signed an informed consent form prior to their participation in the study and they were followed for 4 weeks. An independent rehabilitation doctor who did not participate in clinical management was kept blind to the patients' treatment allocation, carried out the follow-up visits on days 7, 14, and 28 of the treatment, and conducted the pain assessment.

Participants

A total of 120 outpatients were recruited primarily through Good Doctor Online (http://www.HaoDF.com). These subjects were diagnosed with unilateral, dermatomal pain related to herpes zoster (HZ) on the torso lasting for 30 days or more after onset of rash. To be included in the trial, subjects had to be at least 50 years old and experienced SHN for less than 120 days after the onset of vesicles. Furthermore, they had to experience cutaneous and/or subcutaneous pain on the unilateral trunk dermatome or in immediately adjacent cutaneous dermatomes temporally and spatially associated with their HZ rash and a "worse pain" score of 4 or higher on an 11-point pain intensity numerical rating scale (NRS) in the past 24 hours. Subjects were excluded from the study for the following reasons: unilateral dermatome pain in the vesicular region for less than 30 days after onset of rash with diffusely distributed neuropathic pain or significant pain outside the target regions; any clinically significant medical condition or laboratory abnormality; and any cognitive impairment. During the study, subjects were not permitted to use any topical agent or nerve blockers for the affected or adjacent dermatomes within 10 days prior to the baseline visit. However, they were allowed to continue oral analgesics previously used for pain relief at the same dosages they had been using. Further, they were not allowed to change medications and were permitted only to reduce the dose or stop using it during the course of the study.

Randomization

An independent physician carried out the randomization procedure. Subjects were randomly allocated (based on a random number generator) to three groups. Numbers were assigned only once, and no subject was randomized into the study more than once.

Given the nature and the color of the injection, it was impossible to blind the physician and subjects as to the randomization assignments. However, they were informed that these treatment approaches were valid interventions that had a realistic chance of being beneficial and that no approach was known to be more effective than the other. The physician was also instructed to treat subjects in all the three groups with the same degree of rigor, enthusiasm, and optimism. The subjects were advised not to inform the observer about the treatment they received. The effectiveness of the blinding was checked in a sample of 12 subjects by letting the rehabilitation doctor fill in a forced-choice item indicating their treatment allocation.

Sample Size

According to previous studies [24,25] on HZ in outpatients older than 50 years, about 70% of placebo recipients experienced pain 30 days after the onset of rash, whereas more than 40% had pain for 120 days. The expected proportion of pain intensity NRS scores of three or lower for the 28-day treatment was 70%, with a two-sided 5% significance level and assuming an α error of 0.05. Given an anticipated dropout rate of 10%, a minimum of 30 subjects per group were needed for 90% statistical power.

Intervention

All subjects had received antiviral agents (including 800 mg of oral acyclovir, five times daily, or 300 mg of valaciclovir, twice daily) as prescribed by their dermatologist for a total of 7 days upon rash onset. The patients did not use these medications before the baseline visit for study enrollment. The randomized subjects were

categorized into three different groups: the injected MeB_{12} (MB) group, the effective controlled (OT) group, and the control (LD) group, which were given a MeB_{12} (1.00 mg/ 2 mL) local subcutaneous injection (N = 33), 0.5 mg of MeB_{12} tablet three times daily (N = 33), and 2 mL of lidocaine (1%) local subcutaneous injection (N = 32), respectively.

Local subcutaneous injection was administered once daily every morning, between 8 and 11 o'clock, six times per week, for 4 weeks. Using sterile hypodermic (25 gauge) needles and syringes, 0.5 mL each liquid agent was injected at up to four painful areas of torso, based on the subjects' report of their pain experience. After the first injection, the subjects were monitored for any possible symptoms of discomfort and discharged after 1 hour.

Measurements

The outcome measures of this study were consistent with the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials guidelines [26]. All subjects underwent a structured interview to assess the clinical and phenomenological characteristics of their pain: location, descriptive characteristics, intensity changes in pain scores as NRS, the Patients' Global Impression of Change (PGIC) scale, the proportion of subjects with pain ≤3, the average pain score at end point, the proportion of subjects that stopped using analgesics, interference with activities of daily living (ADL) and health-related quality of life (QoL) using the Zoster Brief Pain Inventory (ZBPI) and EuroQoL visual analog scale (VAS).

The primary outcome measures were the overall pain intensity from baseline to days 7, 14, and 28 of the treatment period. Subjects rated the variables of their worst perceived pain during the previous day at the baseline visit and on the day of assessment using an 11-point Likert-type pain intensity scale (NRS; 0 being no pain, 10 being pain as bad as you can imagine), indicating the number that best described their worst pain over the previous 24 hours. Such ratings of daily worst pain intensity provided the basis for analysis of the primary efficacy in the treatment trial. Zoster-related pain is generally described as continuous spontaneous pain, paroxysmal pain [5], tactile allodynia (lightly touching the skin-induced pain [13]), and paresthesia (intense pruritus [27,28]). Changes in various characteristics of the pain and discomfort related to SHN were also measured using an 11-point Likert scale.

Using the PGIC scale, all subjects rated their perceived overall change in pain characteristics since the baseline assessment. PGIC was classified as "very much improved," "much improved," "slightly improved," "no change," "slightly worsened," "much worsened," and "vastly worsened." A rating of "much improved" with the PGIC scale is considered equal to a reduction of two units or approximately 30% in the NRS, whereas that of "very much improved" equals four units or a reduction of approximately 50% [29]. Pain reduction rates of 30% or higher and 50% or higher from baseline have been demonstrated to be clinically important in acute and chronic pain clinical trials [30].

The secondary efficacy measures were to assess interference with ADL and health-related QoL using the ZBPI and EuroQoL VAS after the 4-week treatment period. The ZBPI ADL and QoL scores were used to measure selected activities of daily living and health [31], which included the interference of HZ-related pain with seven ADL and QoL components: general activity, mood, walking ability, normal work, relationship with others, sleep, and enjoyment of life. These items measured pain-related interference over seven health status domains using an 11-point Likert scale, with scores ranging from zero (does not interfere) to 10 (complete interference). The EuroQoL VAS [32] is a validated measure of health-related QoL. The VAS asks participants to rate their current health state on a scale of zero (worst imaginable health state) to 100 (best imaginable health state).

Adverse Events

Adverse events were measured in both groups using two methods: The first method involved the treating physician finding any adverse events occurring during the treatment period and immediate reporting of such adverse events to a researcher. The researcher then recorded the data on standardized clinical notes for each participant. The second method involved the administration of follow-up questionnaires containing an open question that asked the subjects to describe any adverse, harmful, or unpleasant effects that they attributed to the intervention.

Participant Compliance

The treating physician recorded the number of treatment sessions attended by each participant and the number of missed or canceled appointments. The treating physician also reviewed participant's compliance with their personal physician's prescription medication at each visit via collecting back the empty pill kit.

Statistical Analysis

The primary measure variables were the averages of the overall pain intensity ratings of pain scores from previous day (24 hours prior) of baseline visit, and on days 7, 14, and 28 of the treatment period. The repeated measures analyses of variance were used to evaluate the effect of time, group, and time per group interaction for the pain scores after treatment. The method of Bonferroni was used to compare the pain intensity from each measuring time point during the treatment period with that of baseline measurement in the same treated group. Least significant difference (LSD) for multiple comparisons was used to estimate treatment effects in all three groups. Treatment group comparisons for the proportions of subjects who achieved 30% or 50% of pain reduction from the baseline pain scores, the worst pain score ≤3, and "stopped using oral analgesics at end point" were performed using Kruskal–Wallis analysis of variance. The ZBPI scores and

EuroQoL VAS scores were analyzed using analysis of variance. All data were analyzed on an intention-to-treat basis, with the missing data imputed by carrying forward the last available observed value. Two-tailed *P* values less than 0.05 were considered as statistically significant. All analyses were carried out using R software (R 2.15.0 version developed by Peter Dalgaard [Associate professor, Department of Biostatistics, University of Copenhagen, Denmark] of the R Core Development team).

Results

A total number of 120 subjects with SHN were selected during the 8-month enrollment period. Twenty-two subjects were excluded for various reasons, leaving 98 subjects who met the inclusion/exclusion criteria and thus eligible for the trial. Subject disposition is presented in Figure 1, and baseline characteristics of the sample are presented in Table 1. All the 98 subjects who participated in this study were analyzed for their therapeutic response.

Primary Outcomes

Overall Pain Intensity

For overall pain, the MB group showed a significant response after 7 days of local injection ($P < 0.001$), while the OT and LD group showed after 14 days of treatment

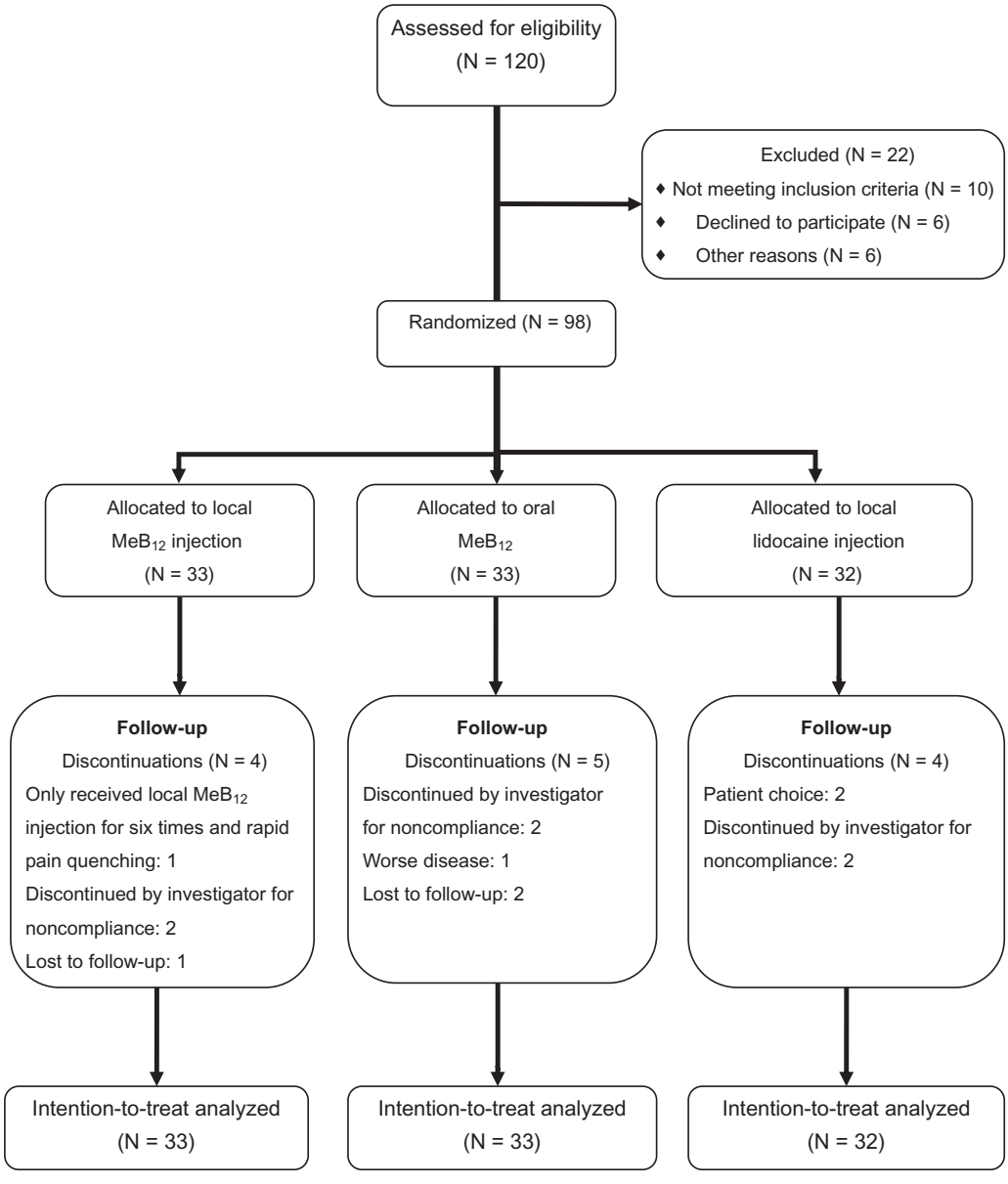

Figure 1 Patient flow diagram. Time from randomization to the study end point was 28 days.

Table 1 Demographic and clinical characteristics of treated patients at baseline

Measures	MB Group (N = 33)	OT Group (N = 33)	LD Group (N = 32)
Age at rash onset (SD)	66.82 (7.78)	67.21 (9.37)	66.75 (10.98)
Female gender (%)	18 (54.55)	16 (48.48)	17 (53.13)
High school or higher educational level (%)	26 (78.79)	25 (75.76)	24 (75.00)
Duration of pain after rash onset (SD), day	57.45 (23.32)	53.15 (19.07)	53.47 (24.21)
Pain NRS at baseline (SD)	6.9 (1.5)	6.9 (1.1)	7.1 (1.6)
Analgesics	27	29	29
Gabapentin	11	10	11
Pregabalin	4	3	3
Amitriptyline	3	6	5
Oxycodone	4	4	4
Tramadol	5	6	6

Data presented are means (SD) or numbers (%).
SD = standard deviation; NRS = numerical rating scale (pain intensity measured on 0–10); MB = the local methylcobalamin injection group; OT = the oral methylcobalamin group; LD = the local lidocaine injection group.

($P < 0.05$) compared with baseline. In the intention-to-treat population, time per group interaction, the different treatment group effect, and the time effect were statistically significant ($P < 0.05$) among the three groups. LSD revealed that the MB group had continuously declined mean worst pain scores at day 7 (5.8 ± 1.4, $P < 0.05$), day 14 (4.6 ± 1.5, $P < 0.001$), and day 28 (3.2 ± 1.6, $P < 0.001$) compared with the other groups. The reduction difference between the OT group and the LD group, however, was not found for any of the three time points. A mean diagram analyzes the tendency of repeated measurements and direct observation of the number of changes as shown in Figure 2. The group comparisons for the proportions of subjects who achieved 30% or 50% of pain reduction, perceived worst pain score ≤3, and "stopped using analgesics at endpoint" are shown in Table 2.

Other Different Categorized Pain Intensities

Although 59, 46, 45, and 32 subjects (in the sample of 98 subjects) complained of continuous spontaneous pain, paroxysmal pain, tactile allodynia, and paresthesia, respectively, the severity of these subtypes did not significantly differ among groups. These scores as assessed by an 11-point NRS revealed that in time per group interaction, the different treatment group effects were statistically significant ($P < 0.05$), except paresthesia. Only in the MB group was the time effect of continuous spontaneous pain, paroxysmal pain, tactile allodynia at three time points vs baseline statistically significant ($P < 0.05$), except paresthesia. A significantly different effect of continuous spontaneous pain was observed in the MB group compared with those in the other group at each time point ($P < 0.05$). Further, the effect of paroxysmal pain and tactile allodynia in the MB group was found significantly different compared with those in the LD group at each time point ($P < 0.05$) and after the 14-day treatment in the OT group ($P < 0.05$). No treatment effect for paresthesia for any of the three time points was observed among the three groups. The reduction differences of these subtypes between the OT group and the LD group, however, were not found at the end of the treatment period. Changes in the categorized pain intensities based on the timeline after different drug applications are shown in Figures 3–6.

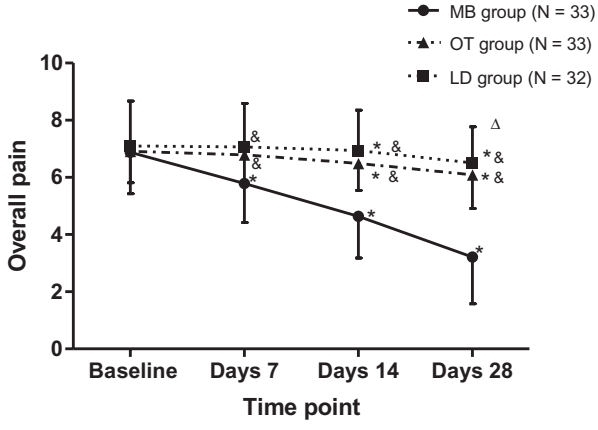

Figure 2 Mean of overall pain at each time point for the 28-day treatment period. The repeated measures analyses of variance were used to evaluate the effect; Δ, time per group interaction, $P < 0.05$; *, pain score at each time point vs the baseline in the same group, $P < 0.05$; and &, pain score in different group of each time that could be compared with that in the MB group, $P < 0.05$. MB = the local methylcobalamin injection group; OT = the oral methylcobalamin group; LD = the local lidocaine injection group.

Table 2 Comparisons of the overall improvement among three groups

	MB Group (N = 33)	OT Group (N = 33)	LD Group (N = 32)	*P*
<30% pain reduction from baseline (%)	3 (9.09)	23 (69.69)	23 (71.88)	
≥30% pain reduction from baseline (%)	10 (30.30)	9 (27.27)	9 (28.12)	<0.001
≥50% pain reduction from baseline (%)	20 (60.60)	1 (3.03)	0 (0.00)	<0.001
Subjects with pain NRS ≤ 3 at end point	24 (72.73)	2 (6.06)	4 (12.50)	<0.001
Pain NRS at end point (SD)	3.2 (1.6)	6.1 (1.2)	6.5 (1.3)	<0.001
The number of using analgesics at baseline (%)	27	29	29	
The number of using analgesics at end point (%)	3	25	26	<0.001
Gabapentin	2	9	11	
Pregabalin	0	3	3	
Amitriptyline	1	4	2	
Oxycodone	0	3	4	
Tramadol	0	6	6	

Data presented are mean (SD) or numbers (%).Treatment group comparisons for the proportions of subjects who achieved 30% or 50% of pain reduction, the number of pain NRS ≤ 3, and the use of analgesics at end point were performed by Kruskal–Wallis analysis of variance. Pain intensity at end-point comparison was used analysis of variance.
SD = standard deviation; NRS = numerical rating scale (pain intensity measured on 0–10). MB = the local methylcobalamin injection group; OT = the oral methylcobalamin group; LD = the local lidocaine injection group.

Secondary Outcomes

The difference in the average scores for ADL and QoL based on the ZBPI and EuroQoL VAS for the 28-day assessment among groups is shown in Figures 7 and 8. After the 28-day treatment, subjects in the MB group had lower scores for ADL and QoL in the ZBPI and higher EQ-QoL scores than those in the OT group. Those

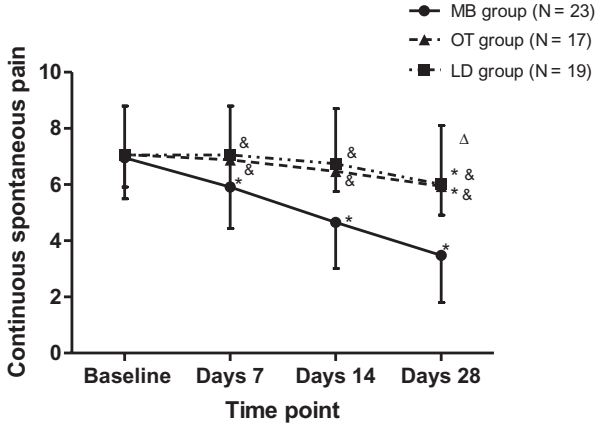

Figure 3 Mean of continuous spontaneous pain at each time point for the 28-day treatment period. The repeated measures analyses of variance were used to evaluate the effect; Δ, time per group interaction, $P < 0.05$; *, pain score at each time point vs the baseline in the same group, $P < 0.05$; and &, pain score in different group of each time that could be compared with that in the MB group, $P < 0.05$. MB = the local methylcobalamin injection group; OT = the oral methylcobalamin group; LD = the local lidocaine injection group.

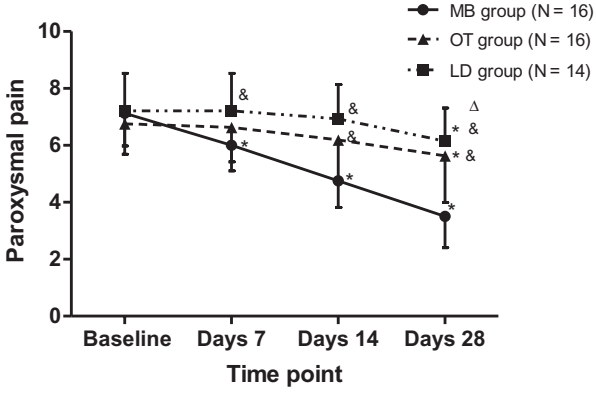

Figure 4 Mean of paroxysmal pain at each time point for the 28-day treatment period. The repeated measures analyses of variance were used to evaluate the effect; Δ, time per group interaction, $P < 0.05$; *, pain score at each time point vs the baseline in the same group, $P < 0.05$; and &, pain score in different group of each time that could be compared with that in the MB group, $P < 0.05$. MB = the local methylcobalamin injection group; OT = the oral methylcobalamin group; LD = the local lidocaine injection group.

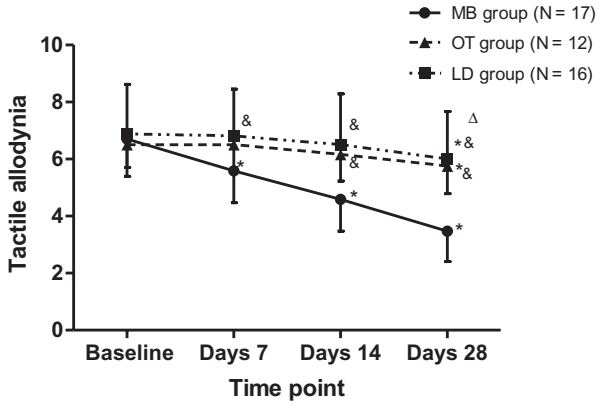

Figure 5 Mean of tactile allodynia at each time point for the 28-day treatment period. The repeated measures analyses of variance were used to evaluate the effect; Δ, time per group interaction, $P < 0.05$; *, pain score at each time point vs the baseline in the same group, $P < 0.05$; and &, pain score in different group of each time that could be compared with that in the MB group, $P < 0.05$. MB = the local methylcobalamin injection group; OT = the oral methylcobalamin group; LD = the local lidocaine injection group.

differences were statistically significant. In contrast, these items in subjects treated with oral MeB_{12} vs lidocaine were not significantly different.

Complications

Of the four subjects in the MB group who did not complete the trial, one dropped out because pain was rapidly quenched after receiving the sixth local MeB_{12} injection, two were discontinued from the trial due to noncompliance after receiving the seventh and tenth local MeB_{12} injections, respectively. Another subject was discontinued after receiving only the third injection. From the OT group, two subjects were dropped due to noncompliance after receiving the fifth treatment; one withdrew because of congestive heart failure after 1 week of treatment, while two were lost to follow-up after the twelfth and sixteenth treatments. From the LD group, two subjects did not complete the study due to lack of improvement after the sixth treatment, whereas another two were discontinued due to noncompliance after receiving the sixth treatment.

Safety of Treatment Procedure

The injections were well tolerated by majority of the subjects. Serious side effects, such as acute lidocaine intoxication, excessive sensory loss, or paresthesia, were not recognized in the LD group. Mild side effects were reported in seven patients with local lidocaine injection, consisting of local irritation (N = 3), local flare (N = 3), and mild weakness (N = 1). One patient in the MB group complained of redness on the face in one occasion. Twelve subjects from the MB group and 10 from the LD group had bleeding and bruises at local injected sites, but bleeding stopped after 1 minute and bruises subsided within 7 days. These were only few minimal adverse events, which disappeared within few hours without any medication. No substantial changes in blood pressure or pulse rate were found in any of the subject in all three treatment groups.

One patient withdrew from the study in the OT group because of hospitalization due to difficulty in breathing at night caused by congestive heart failure, which was judged not to be directly caused by the OT intervention.

Discussion

Our results indicated that the overall pain reduction with oral MeB_{12} is statistically significant after the 28-day treatment. However, only 1 of the 33 (3.03%) subjects achieved pain reduction of ≥50%. The average of pain score was 6.1 ± 1.2, while two had pain score ≤3 and four subjects stopped using analgesics after the 28-day treatment. This is considerably lower than the known reports where in HZ, pain resolved within 120 days following rash onset in more than 20% subjects in antiviral trial placebo groups [33], making it difficult to distinguish between the significant benefits of oral MeB_{12} and spontaneous recovery. In contrast with oral MeB_{12}, the local MeB_{12} injection relieved pain with SHN effectively enough. The severity of pain decreased substantially in the first

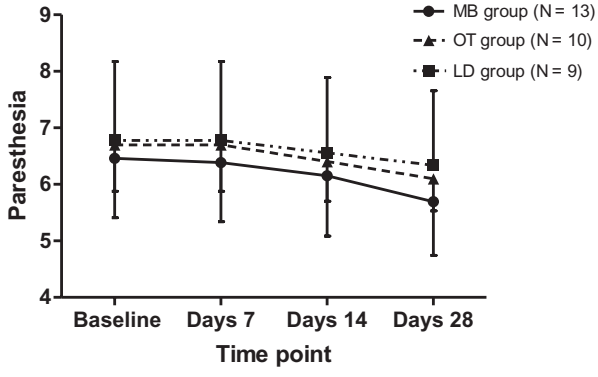

Figure 6 Mean of paresthesia at each time point for the 28-day treatment period. The repeated measures analyses of variance were used to evaluate the effect. Time per group interaction effect, group effect, and time effect were no significance. MB = the local methylcobalamin injection group; OT = the oral methylcobalamin group; LD = the local lidocaine injection group.

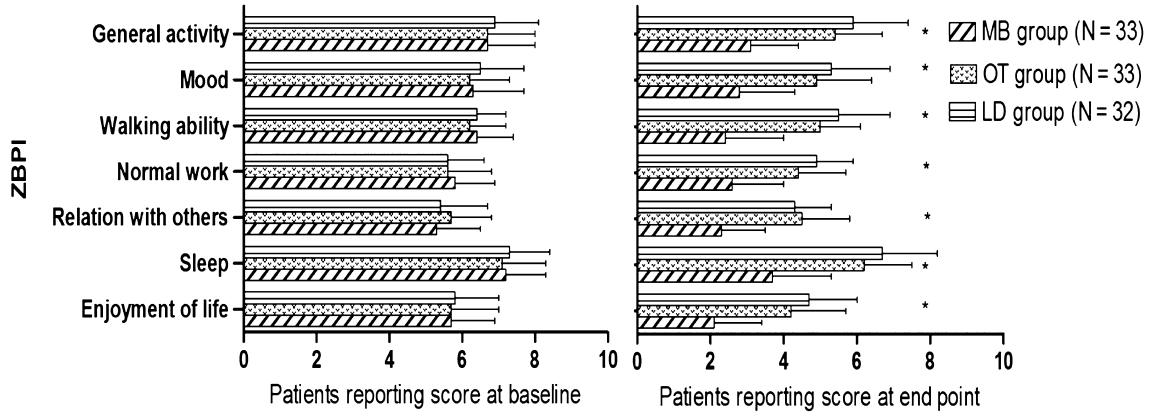

Figure 7 Comparisons of activities of daily living (ADL) and quality of life (QoL) scores in Zoster Brief Pain Inventory (ZBPI) before and after treatment. Comparisons among groups used analysis of variance, *, $P < 0.05$. MB = the local methylcobalamin injection group; OT = the oral methylcobalamin group; LD = the local lidocaine injection group.

week of treatment and continued to decline until the end point of treatment period (28th day). The clinical importance of the pain relief that occurred with local MeB_{12} injection during the 28th day of treatment is supported by the more than 60% of subjects who obtained pain reductions of ≥50% from baseline. The average pain score was 3.2 ± 1.6, while 24 subjects had overall pain score ≤3 and another 24 subjects stopped using analgesics at the end point. ADL and QoL based on the ZBPI and EuroQoL VAS data for 4-week treatment period was consistent with a significant benefit (Table 2, Figures 7 and 8). Only a small number of studies on the use of Cbl for postherpetic neuralgia had been reported [34–37], notably with two publications in the 1950s that negated its clinical efficacy

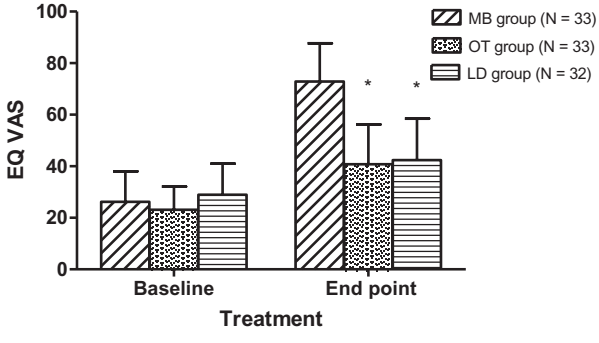

Figure 8 Comparisons of EuroQoL VAS before and after treatment. EuroQoL = Euro quality of life visual analog scale. * VAS score in different group at the end of treatment period compared with that in the MB group, $P < 0.05$. MB = the local methylcobalamin injection group, OT = the oral methylcobalamin group, LD = the local lidocaine injection group.

[36,37]. The strategy, which our study adopted, was based on the following evidence. On one hand, human Cbl deficiency is fairly a common condition [38], some Cbl-deficient patients may have serious neurological dysfunction, even when they have no recognizable hematological abnormalities [39,40]. Cbl has been applied mainly in the treatment of peripheral neuropathy for many years [41–44], although effectiveness of oral Cbl in reversing neurological abnormalities has yet to be established [18], and systemic MeB_{12} administration has had limited success, which may be explained by the Cbl uptake pathway which consists of a series of proteins and receptors [45]. Due to limited uptake capacity, gastrointestinal degradation, or high background uptake by healthy tissues [46], variability in dose responses to oral Cbl among individuals, especially across aging populations, may be attributed to slowed uptake [47]. In PHN skin, there was a marked reduction in the density of epidermal nerve fibers and almost complete disappearance of the subepidermal nerve plexus [12,13]; therefore our strategies should be particularly focused on the local subcutaneous neural endings of the most painful area. The results from this study demonstrated that local subcutaneous injection of MeB_{12} provided a more significant analgesic effect on the painful area with SHN compared with oral MeB_{12}. Local administration of high concentrations of Cbl could directly deliver MeB_{12} to VZV-damaged topical subcutaneous and neuronal tissue, thus restoring neurological responses. However, the neurotrophic and repairing effects of Cbl is difficult to explain given that local injection of MeB_{12} produced a significant analgesic effect so quickly (within 7 days), implying that the effects of Cbl on the most painful site may involve other mechanisms. Our results are supported by the findings of Okada et al. [16].

Surviving but damaged cutaneous nociceptor fibers by VZV in the area of pain may in part be due to accumulation of sodium channels at the injury sites [48–50]. We

expected that lidocaine would be efficacious in relieving pain or allodynia with SHN on the basis of multiple randomized clinical trials that have demonstrated the efficacy of lidocaine patch in patients with PHN [51–53]. In the LD group, the average overall pain, tactile allodynia, ADL and QoL based on the ZBPI and EuroQoL VAS data for 4-week treatment period was consistent with a significant benefit compared with baseline. Nonetheless, only 4 of the 32 (12.50%) subjects achieved worst pain score ≤ 3, the average pain score was 6.5 ± 1.3, and three subjects stopped using analgesics at the end of the treatment period. In this study, lidocaine injection could produce a transient reduction in tactile allodynia, which only lasted 30 to 40 minutes. Our study showed that lidocaine did not provide more persistent and significant pain or allodynia relief than those by oral MeB_{12}. Compared with the lidocaine patch (5%) [51–53], local injection of small dose of lidocaine (1%, 2 mL) once a day could not produce a sustained analgesic effect. It was difficult to distinguish between the significant benefits of local lidocaine injection and spontaneous recovery.

Subjects with SHN generally report various characteristics of pain and discomfort related to herpetic neuralgia [5,54]. The common types include continuous spontaneous pain, paroxysmal pain, tactile allodynia (touch-induced pain) [13], and paresthesia (intense pruritus [27,28]). These symptoms may involve distinct pathophysiological mechanisms. The results from present study show that the mean of continuous pain, paroxysmal pain, and tactile allodynia decreased significantly in the MB group compared with those in the OT group after the 14-day treatment. Within the MB group, the sustained pain reduction over time revealed a significant effect (Figures 3–5). Over the 4-week treatment period, the continuous pain, paroxysmal pain, and tactile allodynia significantly reduced compared with baseline both in the LD and OT groups (Figures 3–5). Alleviation of the three subcategorized pain in the LD group did not differ significantly from those in the OT group at the end of the treatment period, and both the degree of reduction were limited. This implies that benefits from the two treatments in the LD and OT group were both difficult to distinguish from spontaneous recovery. For intense pruritus, although the average of paresthesia after the 28-day treatment revealed a significant effect compared with baseline, treatment with MeB_{12} injection did not result in significant reduction of paresthesia compared with those in the other groups at the end of treatment period. This suggested that Cbl has less effect on stubborn itching than the other subcategorized pain characteristics and discomfort (Figure 6).

This study also evaluated pain interference with the subject's ADL, in congruence with other studies. The subjects in the MB group experienced less interference with their ADL and had better health status than the subjects in the other groups at the end of treatment period. Data analysis revealed that the MB group subjects had a significant reduction in pain interference with ADL and QoL improvement.

The main limitations of this study were the difficulties in blinding local injection. An independent rehabilitation physician who did not participate in clinical management and kept blind to treatment allocation conducted the pain assessment. This effectively prevented un-blinding of the treatment. As the worst pain associated with HZ are the partial lesion regions innervated by distal nerve branches instead of the entire nerve distribution area [24,55], we used subcutaneous injection rather than the nerve blockade technique. An optimal effect was not found (assuming it exists) more likely because the maximum dose of Cbl injected was 1.0 mg/day, which was possibly not sufficient enough to relieve pain in relatively large areas affected by HZ. Although other neurotrophic agents may also be efficacious, whether our results can be extrapolated to other neurotrophic agents (e.g., vitamin B_1, nerve growth factor, or basic fibroblast growth factor) is unknown.

Conclusions

The findings of this 4-week single-center, randomized controlled trial suggest that Cbl is efficacious in reducing the pain and discomfort in SHN-affected patients. Local subcutaneous injection of MeB_{12} appears to be more effective than systemic administration and generally safe for older individuals. The results of this clinical trial lay the foundation for the evidence-based treatment of SHN. First-line therapy for SHN should include strategies using neurotrophic agents. These findings are needed to be confirmed through further studies.

References

1 Quinlivan M, Breuer J. Molecular studies of varicella zoster virus. Rev Med Virol 2006;16:225–50.

2 Gilden D, Mahalingam R, Nagel MA, et al. Review: The neurobiology of varicella zoster virus infection. Neuropathol Appl Neurobiol 2011;37:441–63.

3 Esiri MM, Tomlinson AH. Herpes zoster. Demonstration of virus in trigeminal nerve and ganglion by immunofluorescence and electron microscopy. J Neurol Sci 1972;15:35–48.

4 Haanpaa M, Laippala P, Nurmikko T. Allodynia and pinprick hypesthesia in acute herpes zoster, and the development of postherpetic neuralgia. J Pain Symptom Manage 2000;20:50–8.

5 Niv D, Maltsman-Tseikhin A. Postherpetic neuralgia: The never-ending challenge. Pain Pract 2005;5:327–40.

6 Arani RB, Soong SJ, Weiss HL, et al. Phase specific analysis of herpes zoster associated pain data: A new statistical approach. Stat Med 2001;20:2429–39.

7 Desmond RA, Weiss HL, Arani RB, et al. Clinical applications for change-point analysis of herpes zoster pain. J Pain Symptom Manage 2002;23:510–16.

8 Helgason S, Petursson G, Gudmundsson S, et al. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: Prospective study with long term follow up. BMJ 2000;321:794–6.

9 Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. Clin Infect Dis 2007;44:S1–26.

10 Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352:2271–84.

11 Zaichick SV, Bohannon KP, Smith GA. Alphaherpesviruses and the cytoskeleton in neuronal infections. Viruses 2011;3:941–81.

12 Oaklander AL. The density of remaining nerve endings in human skin with and without postherpetic neuralgia after shingles. Pain 2001;92:139–45.

13 Petersen KL, Rice FL, Farhadi M, et al. Natural history of cutaneous innervation following herpes zoster. Pain 2010;150:75–82.

14 Whitley RJ, Volpi A, McKendrick M, et al. Management of herpes zoster and post-herpetic neuralgia now and in the future. J Clin Virol 2010;48:S20–8.

15 Dror DK, Allen LH. Effect of vitamin B_{12} deficiency on neurodevelopment in infants: Current knowledge and possible mechanisms. Nutr Rev 2008;66:250–5.

16 Okada K, Tanaka H, Temporin K, et al. Methylcobalamin increases Erk1/2 and Akt activities through the methylation cycle and promotes nerve regeneration in a rat sciatic nerve injury model. Exp Neurol 2010; 222:191–203.

17 Inada M. Tissue distribution of vitamin B_{12} and its dynamics in nervous tissues. Nihon Rinsho 1999; 57:2307–12.

18 Solomon LR. Disorders of cobalamin (vitamin B_{12}) metabolism: Emerging concepts in pathophysiology, diagnosis and treatment. Blood Rev 2007;21:113–30.

19 Duyvendak M, Veldhuis GJ. Oral better than parenteral supplementation of vitamin B_{12}. Ned Tijdschr Geneeskd 2009;153:B485.

20 Butler CC, Vidal-Alaball J, Cannings-John R, et al. Oral vitamin B_{12} versus intramuscular vitamin B_{12} for vitamin B_{12} deficiency: A systematic review of randomized controlled trials. Fam Pract 2006;23:279–85.

21 Yaqub BA, Siddique A, Sulimani R. Effects of methylcobalamin on diabetic neuropathy. Clin Neurol Neurosurg 1992;94:105–11.

22 Ide H, Fujiya S, Asanuma Y, et al. Clinical usefulness of intrathecal injection of methylcobalamin in patients with diabetic neuropathy. Clin Ther 1987;9:183–92.

23 Solomon LR. Oral pharmacologic doses of cobalamin may not be as effective as parenteral cobalamin therapy in reversing hyperhomocystinemia and methylmalonic acidemia in apparently normal subjects. Clin Lab Haematol 2006;28:275–8.

24 Dworkin RH, Gnann JW, Jr, Oaklander AL, et al. Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. J Pain 2008;9: S37–44.

25 Watson CPN, Gershon AA. Herpes Zoster and Postherpetic Neuralgia, 2nd rev. and enlarged edition. New York: Elsevier; 2001.

26 Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19.

27 Semionov V, Shvartzman P. Post herpetic itching—A treatment dilemma. Clin J Pain 2008;24:366–8.

28 Oaklander AL. Neuropathic itch. Semin Cutan Med Surg 2011;30:87–92.

29 Farrar JT, Young JP, Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–58.

30 Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.

31 Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials: Adaptation of the Brief Pain Inventory. J Pain 2004; 5:344–56.

32 EuroQol Group. EuroQol—A new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16:199–208.

33 Wood MJ, Kay R, Dworkin RH, et al. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: A meta-analysis of placebo-controlled trials. Clin Infect Dis 1996;22:341–7.

34 Kaipainen WJ. Vitamin B_{12} in zoster neuralgia. Duodecim 1994;110:1789–91.

35 Rabinstein S, Bumaguin De Rabinstein S. Action of vitamin B-1 and B-12 in massive doses in posterpes zoster neuralgia. Sem Med 1962;121:158–61.

36 Helle J, Ohela K. Treatment of herpes zoster neuralgia with massive doses of vitamin B_{12}. Ann Med Exp Biol Fenn 1955;33:116–21.

37 Heaton JM. Vitamin B_{12} and herpes zoster ophthalmicus. Br J Ophthalmol 1959;43:438–9.

38 Healton EB, Savage DG, Brust JC, et al. Neurologic aspects of cobalamin deficiency. Medicine 1991; 70:229–45.

39 Karnaze DS, Carmel R. Neurologic and evoked potential abnormalities in subtle cobalamin deficiency states, including deficiency without anemia and with normal absorption of free cobalamin. Arch Neurol 1990;47:1008–12.

40 Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 1988;318:1720–8.

41 Zhang YF, Ning G. Mecobalamin. Expert Opin Investig Drugs 2008;17:953–64.

42 Kong X, Sun X, Zhang J. The protective role of Mecobalamin following optic nerve crush in adult rats. Yan Ke Xue Bao 2004;20:171–7.

43 Talaei A, Siavash M, Majidi H, Chehrei A. Vitamin B_{12} may be more effective than nortriptyline in improving painful diabetic neuropathy. Int J Food Sci Nutr 2009;60(suppl 5):71–6.

44 Sun Y, Lai MS, Lu CJ. Effectiveness of vitamin B_{12} on diabetic neuropathy: Systematic review of clinical controlled trials. Acta Neurol Taiwan 2005;14:48–54.

45 Quadros EV. Advances in the understanding of cobalamin assimilation and metabolism. Br J Haematol 2010;148:195–204.

46 Petrus AK, Fairchild TJ, Doyle RP. Traveling the vitamin B_{12} pathway: Oral delivery of protein and peptide drugs. Angew Chem Int Ed Engl 2009; 48:1022–8.

47 Clardy SM, Allis DG, Fairchild TJ, et al. Vitamin B_{12} in drug delivery: Breaking through the barriers to a B_{12} bioconjugate pharmaceutical. Expert Opin Drug Deliv 2011;8:127–40.

48 Pappagallo M, Oaklander AL, Quatrano-Piacentini AL, et al. Heterogenous patterns of sensory dysfunction in postherpetic neuralgia suggest multiple pathophysiologic mechanisms. Anesthesiology 2000;92:691–8.

49 Devor M, Govrin-Lippmann R, Angelides K. Na^+ channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. J Neurosci 1993;13:1976–92.

50 Oaklander AL. Mechanisms of pain and itch caused by herpes zoster (shingles). J Pain 2008;9:S10–18.

51 Garnock-Jones KP, Keating GM. Lidocaine 5% medicated plaster: A review of its use in postherpetic neuralgia. Drugs 2009;69:2149–65.

52 Hempenstall K, Nurmikko TJ, Johnson RW, et al. Analgesic therapy in postherpetic neuralgia: A quantitative systematic review. PLoS Med 2005;2:e164.

53 Wolff RF, Bala MM, Westwood M, et al. 5% lidocaine-medicated plaster vs other relevant interventions and placebo for post-herpetic neuralgia (PHN): A systematic review. Acta Neurol Scand 2011;123:295–309.

54 Petersen KL, Rowbotham MC. Natural history of sensory function after herpes zoster. Pain 2010; 150:83–92.

55 Alvarez FK, de Siqueira SR, Okada M, et al. Evaluation of the sensation in patients with trigeminal postherpetic neuralgia. J Oral Pathol Med 2007;36:347–50.