Plasma Vitamin C Is Lower in Postherpetic Neuralgia Patients and Administration of Vitamin C Reduces Spontaneous Pain but Not Brush-evoked Pain

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Objectives: Plasma vitamin C concentrations have been suggested to be related to pain modulation in postherpetic neuralgia (PHN), an intractable neuropathic pain syndrome. In this study, we first compared plasma concentrations of vitamin C between healthy volunteers and PHN patients and then designed a symptom-based and mechanism-based approach to assess the analgesic effect of intravenous vitamin C on spontaneous and brush-evoked pain.

Methods: Study 1 was cross-sectional that enrolled 39 healthy volunteers and 38 PHN patients. Study 2 was a double-blinded, placebo-controlled intervention study, which comprised 41 patients randomly allocated into the ascorbate group and placebo. Each patient received normal saline infusion with or without ascorbate on days 1, 3, and 5 and answered questionnaires that included side effects; numeric rating pain scale (NRS) on spontaneous and brush-evoked pain on days 1, 3, 5, and 7; and patient global impression of change on spontaneous and brush-evoked pain on day 7.

Results: Study 1 revealed that plasma concentrations of vitamin C were significantly lower in patients with PHN than in healthy volunteers ($P < 0.001$). Study 2 showed that ascorbate treatment effectively restored plasma vitamin C concentrations in the patients and decreased spontaneous pain by 3.1 in NRS from baseline to day 7, as compared with a decrease of 0.85 in NRS by placebo treatment ($P < 0.001$). Conversely, ascorbate treatment did not significantly affect brush-evoked pain. Ascorbate treatment also resulted in a better efficacy than placebo in patient global impression of change on spontaneous pain ($P < 0.001$) on day 7 and did not affect brush-evoked pain. No side effects were observed.

Conclusions: Plasma vitamin C status plays a role in PHN, and intravenous ascorbate helps relieve spontaneous pain in PHN.

Key Words: vitamin C, postherpetic neuralgia, mechanism-based, spontaneous pain, brush-evoked pain

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Postherpetic neuralgia (PHN) is a peripheral neuropathic pain syndrome, which occurs in approximately 9% to 13% in herpes zoster (HZ) patients,[1] with older patients (50 y or older) at a higher risk of development.[2] Various symptoms and signs are considered distinct characteristics of neuropathic pain. Certainly, patients with PHN may often have diverse symptoms and signs owing to several different pain mechanisms. On the basis of mechanisms, neuropathic pain exhibits stimulus-evoked pain and spontaneous pain, that is, stimulus independent.[3] Spontaneous pain can be either continuous (persistent) or intermittent (paroxysmal). Stimulus-evoked pain is commonly classified into mechanical, thermal, or chemical. Mechanical hyperalgesias are further classified as brush-evoked (dynamic), pressure-evoked (static), and punctate hyperalgesias.[3] Brush-evoked pain (allodynia, also called dynamic mechanical hyperalgesia) is the most common manifestation of stimulus-evoked pain in patients with PHN.[4,5] The different mechanisms and distinct symptoms can converge in a single patient. Thus far, managing PHN is a clinical challenge owing to variability in individual symptoms, mechanisms, and treatment responses. Therefore, a symptom-based and mechanism-based approach of neuropathic pain, which allows selection of treatment on a more rational basis, has been advocated for clinical management.[5]

Vitamin C is a major water-soluble antioxidant and a coenzyme.[6] A community-based case-control study reveals that lower vitamin C intake significantly increases HZ risk statistically among daily micronutrient intakes.[7] In patients with severe infectious disease, low plasma vitamin C concentrations have been identified.[8] Some PHN patients have been reported to achieve pain relief immediately after mega-doses of intravenous ascorbate.[9] Further, vitamin C reduces the prevalence of complex regional pain syndrome type I, a form of peripheral neuropathic pain syndrome.[10,11] Particularly, ascorbic acid can facilitate β-endorphin secretion from rat hypothalamic neurons in culture.[12] These findings in the literature suggest that vitamin C is related to modulation of neuropathic pain.

In the present study, we first compared plasma concentrations of vitamin C in PHN with those of healthy volunteers. We then designed a symptom-based and mechanism-based approach to investigate whether patients with PHN might respond to the treatment with vitamin C supplementation.[9] Vitamin C (sodium ascorbate) is normally administered intravenously or orally. Because plasma concentrations of vitamin C are tightly controlled by tissue transport, absorption, and excretion, only intravenous administration of vitamin C produces rapid high plasma concentrations.[13] Therefore, we administrated vitamin C

via intravenous route to examine the effect of systemically administered vitamin C on spontaneous pain and brush-evoked pain in patients with PHN.

METHODS

Patients and Study Design

This investigation was approved by the Institutional Ethics Committee of Chi-Mei Foundation Hospital, Tainan, Taiwan. Informed consents were obtained from all patients and control volunteers. All patients were with permission to withdraw from the study at any time.

Study 1 (Cross-sectional Study)

Patients and Control Participants

To explore the relationship between pain severity of PHN and concentration of plasma vitamin C, we recruited 38 PHN patients from the Pain Clinic of Chi-Mei Foundation Hospital, who had persistent pain lasting more than 3 months in the region of the cutaneous vesicular lesions from rash onset, in consistency with the distinction between acute and chronic pain in the International Association for the Study of Pain classification of chronic pain syndromes produced by Merskey and Bogduk in 1994.[2] Control participants were healthy volunteers from the relatives of outpatients or hospital employees. Those who regularly took or were taking antioxidant vitamin supplements right before entry or had an infection or an admission history during the last 3 months were excluded from the control participants of this study.

For each patient, the following information was recorded: age, sex, body height, body weight, duration of pain after healing of the skin rash, poor appetite, insomnia, psychologic distress, and physical disability at first visit to our Pain Clinic. Patients also filled out an 11-point numeric rating pain scale (NRS) (from 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable)[2,14] for the intensity of average daily spontaneous pain and brush-evoked pain elicited by lightly moving a cotton swab across the skin.[5]

Study 2 (Clinical Trial)

Patients

To examine our hypothesis that vitamin C administration may help relieve the pain in PHN patients, we conducted a randomized, double-blinded, placebo-controlled intervention study on outpatients visiting our Pain Clinic. The trial was double-blinded, with the pharmacist being the only individual in possession of the allocation code during the trial. A block randomization (a block of 10 at a time by a random number table) was carried out by our hospital pharmacist. PHN patients who participated in this study received a number starting from number 1 to 41, successively, and the medication was formulated by the pharmacist in advance and was administrated by the nurse. All the patients, nurses, and physicians involved were not aware of the treatment allocation until the end of the trial. Diagnosis ruled out other polyneuropathies, such as patients with compression fracture, spondylolisthesis of the same levels, and diabetic polyneuropathy. We only recruited patients who were 18 years or older and who had PHN for at least 3 months and for a maximum of 2 years and had spontaneous pain rated at least score 4 on NRS. Female patients who were nonpregnant and nonlactating were recruited. Patients were excluded if blood level of uric acid was higher than 7.0, as recommended by Berger et al.[15] During the study, patients were not allowed to receive specific treatments for the relief of PHN. A washout period of 1 week before the inclusion visit was required for the following medications: benzodiazepines, skeletal muscle relaxants, steroids, capsaicin, mexiletine, nonsteroidal anti-inflammatory drugs, and anticonvulsants. Patients were permitted to take acetaminophen as rescue medication at a maximum daily dose of 3.0 g.

Eligible patients were randomly assigned to 1 of the 2 parallel treatment groups that receive intravenous 500 mL normal saline infusion with or without colorless ascorbate (50 mg/kg body weight, maximum dose 2.5 g/d). All patients received 3 intravenous administrations, that is, on days 1, 3, and 5, with an infusion rate of 100 to 150 mL/h. Patients in both groups were requested to answer pain questionnaires that included (1) the intensity of average daily spontaneous pain on 11-point NRS from 0 to 10 (with 0 being no pain at all and 10 being the worst pain imaginable) before the intravenous administrations on days 1, 3, 5, and 7; (2) brush-evoked pain (allodynia) by mechanical stimulation with a cotton swab performed before the intravenous administrations on days 1, 3, 5, and 7 (allodynia was graded on 11-point NRS from 0 to 10); (3) a 7-point categorical scale of patient global impression of change[16] (PGIC) on spontaneous pain (Fig. 1) on day 7; (4) a 7-point categorical scale of PGIC on brush-evoked pain on day 7; and (5) side effects. The primary efficacy measure[17] was the change in the average daily 11-point NRS on spontaneous pain and brush-evoked pain from baseline day 1 to the final day 7. Secondary efficacy measures[17] included a 7-point categorical scale of PGIC on spontaneous pain, brush-evoked pain, and side effects. "Response to treatment" is defined as a change of -2.0 on NRS.[14,18]

Safety Assessment

Safety parameters included the recording of adverse events at each visit from days 1 to 7 and complete physical examination on days 1 and 7. If a patient reported any discomfort during the vitamin C or placebo treatment, we

After this treatment, my overall condition is:

1. ☐ Much improvement
2. ☐ Moderate improvement
3. ☐ Minimal improvement
4. ☐ No change
5. ☐ Minimal worse
6. ☐ Moderate worse
7. ☐ Much worse

FIGURE 1. A 7-point categorical scale (Study 2).

would terminate the treatment immediately and ask the patient to answer the questionnaires and allow blood sampling on day 7.

Pain Evaluation

There are 4 popular methodologies for measuring pain severity: visual analog scales, NRSs, verbal rating scales, and the McGill Pain Questionnaire. Although pain evaluations with visual analog scales were generally used, visual analog scales could be difficult for elder patients to use. The risk of developing PHN after shingles is high after the age of 60 years.[1] This is close to our result that the mean age of patients with PHN is 64.4 with a median age of 67.5 years (Table 1). In clinical trial, it is often important to be efficient and to minimize patient burden when collecting data. Dworkin et al[2] recommended the NRS to be used for assessment of pain severity in patients with PHN. Therefore, we chose the NRSs for assessment of pain severity in our study.

Specimen Collection, Handling, and Biochemical Determination

In Study 1, blood samples drawn from the patients and control participants into lithium heparin vacutainers after overnight fast were transported to the laboratory in a light-excluding container and stored for no more than 6 hours at 4°C before centrifugation.[19,20] In Study 2, blood samples were taken for routine hematology and vitamin C measurement on days 1 and 7 after overnight fast. Separated plasma was stored frozen at −80°C.[20] The automated enzymatic method for analysis of total plasma vitamin C, which refers to the sum of ascorbic acid (C6H8O6) and L-dehydroascorbic acid, was carried out as described by Lee et al,[21] and provided by the Cobas Mira Plus Instrument (Roche Diagnostics, Montclair, NJ).[22]

Statistical Analyses

Data processing and data analysis were performed using SPSS for Windows, Version 10.0.7 (SPSS Inc, Chicago, IL). Significance was accepted at the 5% level. Owing to small sample sizes and lack of fitness to normal distribution for most measurements in this study, we described data as means ± SD and median, and we analyzed them using nonparametric statistics. Mann-Whitney *U* test was used to test the differences between 2 groups and to analyze mean changes from baseline days 1 to 7 in average daily pain intensity of spontaneous pain and that of brush-evoked pain in patients with PHN. Spearman ρ correlation test was used to correlate among age, duration of pain, plasma concentrations of vitamin C, NRS of spontaneous pain, and NRS of brush-evoked pain. Fisher exact test was used to analyze proportion of patients that responded by 30% and 50% on spontaneous pain between 2 groups, patients' PGIC between 2 groups, and 2 conditions in the same group.

RESULTS

Study 1

Between July 2001 and June 2003, 38 patients (25 men and 13 women) with PHN and 39 volunteers (26 men and 13 women) were included. There were no significant differences between volunteer healthy patients and patients with PHN in sex, age, body height, and body weight (Table 1).

Plasma Vitamin C Concentrations in Healthy Controls and Patients With PHN

Table 1 shows that the plasma vitamin C concentrations were significantly lower in patients (4.6 ± 3.1 mg/L) than in controls (13.5 ± 6.0 mg/L) ($P < 0.001$). This difference was independent of sex, age, duration of pain, and NRS of spontaneous pain or brush-evoked pain. Nonetheless, the intensity of spontaneous pain correlated with that of brush-evoked pain in patients with PHN ($r = 0.481$, $P = 0.002$) (Table 2). On the other hand, there was a significant correlation of plasma vitamin C concentrations with NRS of spontaneous pain ($r = -0.387$, $P = 0.016$) but not with that of brush-evoked pain ($r = -0.062$, $P = 0.712$).

Complications Related to PHN

Before the beginning of Study 1, our PHN patients had poor appetite (65.8%), insomnia (68.4%), psychologic distress (84.2%) (eg, depression and anxiety), and physical disability (52.6%). These conditions, which have been reported by others,[23] are common complications of PHN.

Study 2

A summary profile of patients of Study 2 is presented in Figure 2. Between April 2004 and March 2006, a total of

TABLE 1. Comparison of Demographic Characteristics and Vitamin C Profiles Between Healthy Participants and Patients With PHN (Study 1)

	Healthy Group (N = 39)		Patients With PHN (N = 38)		
	Mean (SD)	Median	Mean (SD)	Median	*P*
Sex					
Male	26		25		
Female	13		13		
Age (y)	61.2 (8.6)	61.0	64.4 (23.7)	67.5	0.76
Body height (cm)	161 (9)	161	160 (8)	161	0.826
Body weight (kg)	60 (13)	55	58 (9)	56	0.781
NRS of spontaneous pain	0	0	6.8 (2.2)	8.0	
NRS of allodynia	0	0	3.5 (2.8)	4.0	
Duration of pain (mo)	0	0	16.1 (17.8)	8.0	
Vitamin C (mg/L)	13.5 (6.0)	13.0	4.6 (3.1)	2.9	< 0.001

Statistical differences between the 2 groups are analyzed using Mann-Whitney *U* test.

Duration of pain indicates duration of pain after healing of the herpes zoster skin rash; N, total number of patients; NRS, numeric rating pain scale; PHN, postherpetic neuralgia.

TABLE 2. The Correlation Between Plasma Vitamin C Concentrations, NRS of Spontaneous Pain, and NRS of Brush-evoked Pain in PHN Patients (Study 1)

	Correlation Coefficient (r)	P
Spontaneous pain vs. brush-evoked pain	0.481	0.002
Vitamin C vs. spontaneous pain	−0.387	0.016
Vitamin C vs. brush-evoked pain	−0.062	0.712

Statistical analysis between the 2 groups is analyzed using Spearman ρ correlation method.

NRS indicates numeric rating pain scale; PHN, postherpetic neuralgia.

41 patients were enrolled, among whom 20 patients were randomized to placebo treatment and 21 patients to ascorbate administration. During the treatment, 1 patient from each group withdrew from the study, with a completion rate of 95.1% (39/41), because of lack of efficacy or of minimally worse pain. The data of these 2 patients were included and reported in this study. There were no significant differences between placebo-treated patients and ascorbate-treated patients in sex, age, body weight, body height, and the duration of pain and NRS of spontaneous pain and NRS of allodynia on day1 (Table 3). The plasma concentrations of vitamin C in both groups on day 1 were low and not significantly different. However, ascorbate administration for 1 week markedly raised the plasma vitamin C concentration in the ascorbate-treated group from a mean value of 6.6 to a mean concentration of 12.8 mg/L, that is, essentially the same as that of healthy controls (a mean concentration of 13.5 mg/L, Table 1). When we adjusted the plasma vitamin C values by omitting those of the 2 patients that terminated the treatment (1 from each group), the concentrations of plasma vitamin C in both groups were only slightly affected and the difference between the 2 groups was still highly significant ($P < 0.001$) (Table 3).

Primary Efficacy: Changes of Average Daily NRS in Spontaneous Pain and Brush-evoked Pain on Day 7

As shown in Table 4, the mean change of reducing NRS for spontaneous pain from baseline days 1 to 7 in the ascorbate-treated patients increased to (3.1 ± 1.6), which is significantly higher than that (0.85 ± 1.09) in the placebo-treated patients ($P < 0.001$). By contrast, the means of NRS for brush-evoked pain from baseline days 1 to 7 did not significantly change in either group ($P = 0.192$).

The treatment responder was defined as an individual whose NRS decreased ≥ 2 in their pain from baseline (day 1) to the final day 7.[14] In the ascorbate group, 16 of 21 patients (76.2%) with spontaneous pain were responders, whereas only 4 of 21 (19.0%) patients with brush-evoked

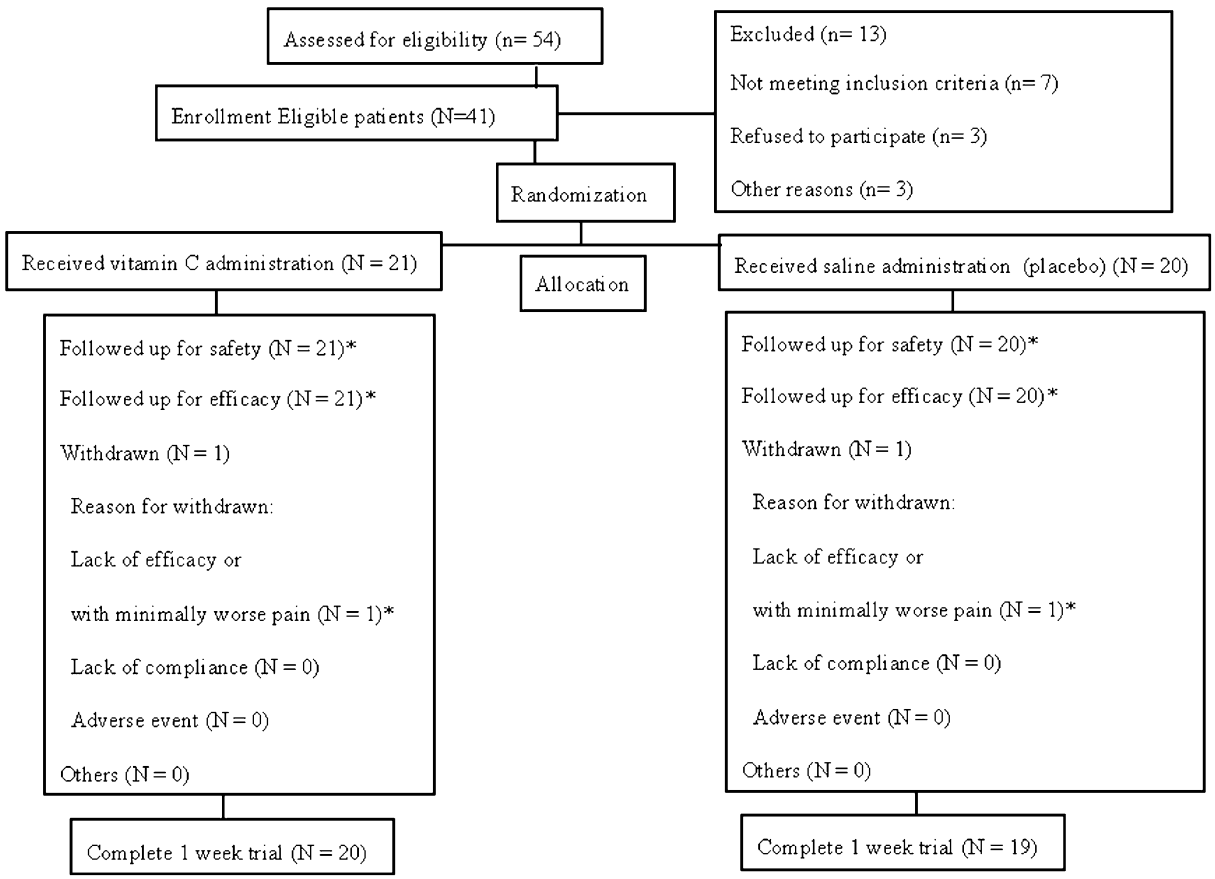

FIGURE 2. Profile of patients with postherpetic neuralgia (PHN) in Study 2. *The patient provided all follow-up efficacy assessment and blood sampling (including the patient who withdrew from the study in each group).

TABLE 3. Patient Characteristics at Inclusion (Study 2)

	Ascorbate Administration (N = 21)		Placebo Treatment (N = 20)		
	Mean (SD)	Median	Mean (SD)	Median	*P*
Sex					
Male	10		11		
Female	11		9		
Age (y)	62.6 (13.8)	67	63.6 (11.4)	68	0.906
Body height (cm)	158.3 (8.9)	160	159.1 (8.6)	161	0.724
Body weight (kg)	56.1 (12.1)	54	55.8 (8.1)	56	0.479
NRS of spontaneous pain (day 1)	7.1 (1.8)	7	6.5 (1.4)	6	0.33
NRS of allodynia (day 1)	3.5 (2.7)	4	3.1 (2.4)	4	0.657
Duration of pain (mo)	5.6 (5.0)	3.0	6.2 (5.2)	4.0	0.404
Vitamin C (mg/L) (day 1)	6.6 (3.3)	6.1	6.0 (2.3)	6.2	0.814
Vitamin C (mg/L) (day 7)	12.8 (3.6)	11.6	5.8 (2.2)	6.0	< 0.001
Vitamin C (mg/L) (day 7)*	12.4 (3.0)	11.4	5.7 (2.4)	5.9	< 0.001

*Data in this row are from the patients that completed the 1-week trial (N = 20 in the ascorbate group and N = 19 in the placebo group).
Statistical analysis between 2 groups is analyzed using Mann-Whitney *U* test.
Duration of pain indicates duration of pain after healing of the herpes zoster skin rash; N, total number of patients; NRS, numeric rating pain scale; PHN, postherpetic neuralgia

pain were responders ($P < 0.001$) (data not shown). As regards the placebo group, 6 of 20 (30%) patients with spontaneous pain were responders, yet, 2 of 20 (10%) patients with brush-evoked pain were responders ($P = 0.235$). Additionally, we also estimated proportion of patients that responded by 30% and 50% on spontaneous pain (Table 5). Two results showed a consistent relationship between > 30% reduction and the reduction of 2 points on spontaneous pain. This observation is similar to a previous study[14] as a reduction of 2 points on NRS is sufficient to confer the improvement on pain, regardless of baseline pain.

In the vitamin C group, 19 of 21 participants took acetaminophen, with a total dose of 2.0 ± 0.9 g on day 1. On day 7, 1 of the 2 patients who did not take acetaminophen turned out to be a responder and the other one a nonresponder. The toal acetaminophen doses were 0.8 ± 0.6 and 1.4 ± 1.5 g for the responders (18/21) and the nonresponders (3/21), respectively, on day 7. Intriguingly, the treatment responders took less rescue medication than those who did not respond to vitamin C.

The number needed to treat for > 30% reduction in pain score was 1.96 (confidence interval: 1.3 to 4.0). Owing to relatively small patient number of our intervention study, more studies are needed to confirm our findings.

TABLE 4. Changes of NRS in Spontaneous Pain and Brush-evoked Pain From Baseline Days 1 to 7 in PHN Patients (Study 2)

Days 7 to 1	Ascorbate Group (N = 21)	Placebo Group (N = 20)	*P*
Spontaneous pain	−(3.1 ± 1.6)	−(0.85 ± 1.09)	< 0.001
Brush-evoked pain	−(0.52 ± 0.75)	−(0.25 ± 0.55)	0.192

Values (mean ± SD) between the 2 groups were analyzed using Mann-Whitney *U* test.
NRS indicates numeric rating pain scale; PHN, postherpetic neuralgia; N, total number of patients.

Secondary Efficacy: Changes of PGIC in Spontaneous Pain and Brush-evoked Pain on Day 7

On day 7, 61.9% patients in the ascorbate-treated group reported "moderate to much improvement" in PGIC of spontaneous pain, as compared with 10.0% patients in the placebo group (Table 6). The overall efficacy of PGIC in spontaneous pain on day 7 was significantly better in the ascorbate treatment than in the placebo treatment ($P < 0.001$). Conversely, the overall efficacy of PGIC in brush-evoked pain was not significantly different between the ascorbate-treated group and the placebo group ($P = 0.66$) (data not shown).

Correlation Between Efficacy and the Initial Plasma Concentration of Vitamin C

Patients with a plasma vitamin C concentration higher than 10.0 mg/L (56.78 μmol/L) are classified as well nourished.[24] In ascorbate-treated group, among the 4 well-nourished patients, only 1 patient produced a positive response (much/moderate/minimal improvement) in spontaneous pain (Table 7). By contrast, of the 17 not-well-nourished patients, 15 showed a positive response in

TABLE 5. Proportion of Patients Who Responded by 30% and 50% on Spontaneous Pain (Study 2)

Reduction in Pain From Baseline	Ascorbate Group (N = 21) (%)	Placebo Group (N = 20) (%)	*P**
< 30%†	3/21 (14.3)	13/20 (65)	0.0008
≥ 30%	5/21 (23.8)	5/20 (25)	
≥ 50%	13/21 (61.9)	2/20 (10)	

*The *P* value (determined using Fisher exact test) represents the overall significance level of reduction in pain from baseline on NRS between the 2 treatment groups.
†Percentage reduction in pain from baseline = 100% × (baseline pain − final pain)/baseline pain.

TABLE 6. Changes of PGIC in Spontaneous Pain in PHN Patients on Day 7 (Study 2)

Efficacy	Ascorbate Group (N = 20) (%)	Placebo Group (N = 21) (%)	*P*
Minimally worse	1 (4.8)	1 (5.0)	< 0.001*
Minimal improvement/no change	7 (33.3)	17 (85.0)	
Much/moderate improvement	13 (61.9)	2 (10.0)	

*The *P* value (determined using Fisher exact test) represents the overall significance level among the 7-point categorical changes of PGIC between the 2 treatment groups.

N indicates total number of patients; PGIC, patient global impression of change; PHN, postherpetic neuralgia.

spontaneous pain (15/17 = 88.2%). There was a significant difference ($P = 0.027$) in the overall response rate between the 2 groups of patients, that is, the well-nourished group and the not-well-nourished group (Table 7).

Adverse Events and the Safety of Infusion Solution

One patient in each group reported of minimally worse pain after the second intravenous infusion and did not receive the third infusion. Both of them completed all questionnaires and blood samplings on day 7. No other patients had any side effects, such as vasculitis or phlebitis.

DISCUSSION

In this study, we first observed that plasma vitamin C concentrations in patients with PHN were significantly lower than those in healthy controls. This may be owing to their original low plasma vitamin C concentration or owing to deterioration of the disease. A community-based case-control study reveals that those with low vitamin C intake are at a significantly higher risk for HZ7 that is caused by reactivation of varicella zoster virus. Vitamin C is the first line plasma antioxidant in the virus-specific cellular immunity, and low plasma vitamin C is found in various infections and in critically ill patients, possibly as a result of the disease processes by the rapid consumption of free radicals.[8] Indeed, plasma vitamin C concentrations are reported to be strongly associated with daily intake of vitamin C, but not significantly affected by age.[24] Another possible cause of low plasma vitamin C in our cases is poor appetite, of which 65.8% of our patients complained, which is common in PHN patients.

TABLE 7. Changes of PGIC in Spontaneous Pain on Day 7 Between Not-well-nourished Patients and Well-nourished Patients with PHN in Ascorbate Group (N = 21) (Study 2)

Efficacy	Not-well-nourished Patients (N = 17)	Well-nourished Patients (N = 4)	*P*
Minimally worse/no change	2	3	0.027*
Much/moderate/minimal improvement	15	1	

*The *P* value (determined using Fisher exact test) represents the overall significance level among the 7-point categorical changes of PGIC between the 2 different vitamin C conditions in ascorbate group.

N indicates total number of patients; PGIC, patient global impression of change; PHN, postherpetic neuralgia.

In Study 2, we administered relatively high doses of ascorbate to our patients to ensure high concentrations of vitamin C in the cerebrospinal fluid (CSF) because the homeostatic transport system for ascorbic acid through the blood-CSF barrier is unfavorable to low plasma vitamin C.[25] We found that administration of ascorbate 3 times in 1 week markedly raised the plasma ascorbate concentration from 6.6 to 12.8 mg/L, that is, essentially the same as that of healthy controls (13.5 ± 6.0 mg/L, Study 1). A slow but marked increase in the ascorbate level in CSF after intravenous infusion of ascorbate has been reported.[26] Here, we demonstrated that intravenous ascorbate administration resulted in a significantly greater mean change of average daily NRS in spontaneous pain from days 1 to 7 than the placebo administration (3.1 vs. 0.85, $P < 0.001$). It has been reported that a change in NRS of -2.0, which is equivalent to a reduction of 30% in the NRS, represents a clinically important difference.[14] By this standard, our placebo-controlled patients have no significant improvement in spontaneous pain, although the 3.1 change in the NRS of our ascorbate-treated patients represents a significant improvement (about 50% reduction in NRS) in spontaneous pain.[14] Moreover, the efficient primary efficacy in NRS was reconfirmed by the better secondary efficacy in PGIC on day 7 in the ascorbate group than in the placebo group for spontaneous pain. On the contrary, that intravenous ascorbate did not significantly affect brush-evoked pain in PHN patients is consistent with our observation in Study 1. As a result, plasma vitamin C concentrations were significantly and inversely correlated with NRS of spontaneous pain but not with that of brush-evoked pain in patients with PHN although the intensity of the 2 types of pain was significantly correlated. This finding is close to a previous study which demonstrated that intravenous magnesium therapy reduces spontaneous pain but not brush-evoked allodynia in patients with PHN.[27] Similarly, a 30-minute intravenous infusion of ketamine has shown to develop a differential effect on spontaneous pain and stimulus-dependent pain in patients with nerve injury pain.[28] This is not surprising because spontaneous pain and brush-evoked pain in individual patients involve different mechanisms.[3]

PHN is one of intractable peripheral neuropathic pain whose mechanisms include disinhibition,[3] central sensitization,[3] reactive oxygen species (ROS),[29] and neuroinflammation.[30] Vitamin C can conceivably intervene in some of the above conditions by several possible mechanisms of action. One mechanism of peripheral neuropathic pain in spontaneous pain (stimulus-independent pain) is "disinhibition" that is mediated by the spinal descending inhibitory pathway.[3] Spinal monoamines (norepinephrine and serotonin) are involved in the descending inhibition of nociceptive transmission.[31] Noradrenergic fibers from brainstem terminate and release norepinephrine in the superficial dorsal horn to exert its antinociceptive actions. Ascorbic acid, a key cofactor of dopamine β-monooxygenase, is essential for norepinephrine biosynthesis. The conversion of dopamine to norepinephrine by dopamine β-monooxygenase is maximally efficient only in cells replete with external

ascorbic acid.[6] Thus, to enhance the spinal descending inhibitory pathway is one of the possible mechanisms of vitamin C to reduce neuropathic pain. Besides, β-endorphin has been reported to elevate the threshold of chronic neuropathic pain in rats.[32] Ascorbic acid, by enhancing the adenylyl cyclase-cyclic adenosine monophosphate system, can augment the production and release of β-endorphin from neonatal rat hypothalamic neurons in culture in a time-related and dose-dependent manner,[12] and hence, may modulate neuropathic pain.

ROS contribute to the development and maintenance of neuropathic pain that can be relieved by systemic injection of an ROS scavenger in a dose-dependent manner in a rat model.[29] Thus, an ROS scavenger is suggested to be neuroprotective by scavenging excess ROS.[29] Indeed, vitamin C is an extracellular and intracellular antioxidant[33] but also the major antioxidant in CSF, and its effect is concentration dependent.[34] Nowadays, exaggerated inflammation[35] after tissue trauma and cumulative neuroinflammation of peripheral nerve system[36] in rats have also been shown to induce spontaneous pain. Not surprisingly, it has been advocated that it may be beneficial to supply and increase plasma concentrations of vitamin C for wrist fracture patients at risk for complex regional pain syndrome type I.[10,11] Thus, patients with PHN may be highly susceptible to vitamin C deficiency, which may constitute a perpetuating factor for chronic neuropathic pain. Therefore, vitamin C may be a suitable adjuvant for inclusion in multidrug regimens to control spontaneous pain in patients with PHN.

In conclusion, we demonstrate that patients with PHN have lower plasma concentrations of vitamin C and that short-term intravenous administration of mega-dose vitamin C helps to relieve their spontaneous pain but not brush-evoked pain. The fact that intravenous ascorbate improves spontaneous pain but does not significantly affect brush-evoked pain in patients with PHN suggests that our findings are not a result of placebo effects. Because of the heterogeneous neuropathic features in PHN patients, a symptom-based and mechanism-based approach of neuropathic pain needs more consideration in tailored treatment and seems promising for clinical management of drug selections.[37]

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REFERENCES

1. Bowsher D. Post-herpetic neuralgia in older patients. Incidence and optimal treatment. *Drugs Aging*. 1994;5:411–418.
2. Dworkin RH, Carrington D, Cunningham A, et al. Assessment of pain in herpes zoster: lessons learned from antiviral trials. *Antiviral Res*. 1997;33:73–85.
3. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353: 1959–1964.
4. Pappagallo M, Oaklander AL, Quatrano-Piacentini AL, et al. Heterogenous patterns of sensory dysfunction in postherpetic neuralgia suggest multiple pathophysiologic mechanisms. *Anesthesiology*. 2000;92:691–698.
5. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. *Neurobiol Dis*. 1998;5:209–227.
6. Levine M, Dhariwal KR, Washko PW, et al. Ascorbic acid and in situ kinetics: a new approach to vitamin requirements. *Am J Clin Nutr*. 1991;54:1157S–1162S.
7. Thomas SL, Wheeler JG, Hall AJ. Micronutrient intake and the risk of herpes zoster: a case-control study. *Int J Epidemiol*. 2006;35:307–314.
8. Schorah CJ, Downing C, Piripitsi A, et al. Total vitamin C, ascorbic acid, and dehydroascorbic acid concentrations in plasma of critically ill patients. *Am J Clin Nutr*. 1996;63: 760–765.
9. Chen JY, Chu CC, So EC, et al. Treatment of postherpetic neuralgia with intravenous administration of vitamin C. *Anesth Analg*. 2006;103:1616–1617.
10. Zollinger PE, Tuinebreijer WE, Kreis RW, et al. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. *Lancet*. 1999;354: 2025–2028.
11. Zollinger PE, Tuinebreijer WE, Breederveld RS, et al. Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study. *J Bone Joint Surg Am*. 2007;89: 1424–1431.
12. Yang Z, Copolov DL, Lim AT. Ascorbic acid augments the adenylyl cyclase-cAMP system mediated POMC mRNA expression and beta-endorphin secretion from hypothalamic neurons in culture. *Brain Res*. 1996;706:243–248.
13. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann Intern Med*. 2004;140:533–537.
14. 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;94:149–158.
15. Berger L, Gerson CD, Yu TF. The effect of ascorbic acid on uric acid excretion with a commentary on the renal handling of ascorbic acid. *Am J Med*. 1977;62:71–76.
16. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial Alzheimer's Disease Cooperative Study. *JAMA*. 2000;283:1007–1015.
17. Rosenstock J, Tuchman M, LaMoreaux L, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain*. 2004;110: 628–638.
18. Salaffi F, Stancati A, Silvestri CA, et al. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain*. 2004; 8:283–291.
19. Chung WY, Chung JK, Szeto YT, et al. Plasma ascorbic acid: measurement, stability and clinical utility revisited. *Clin Biochem*. 2001;34:623–627.
20. Key T, Oakes S, Davey G, et al. Stability of vitamins A, C, and E, carotenoids, lipids, and testosterone in whole blood stored at 4 degrees C for 6 and 24 hours before separation of serum and plasma. *Cancer Epidemiol Biomarkers Prev*. 1996;5: 811–814.
21. Lee W, Roberts SM, Labbe RF. Ascorbic acid determination with an automated enzymatic procedure. *Clin Chem*. 1997;43:154–157.
22. Ihara H, Matsumoto N, Shino Y, et al. An automated assay for measuring serum ascorbic acid with use of 4-hydroxy-2,2, 6,6-tetramethylpiperidinyloxy, free radical and o-phenylenediamine. *Clin Chim Acta*. 2000;301:193–204.
23. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain*. 2002;18:350–354.
24. VanderJagt DJ, Garry PJ, Bhagavan HN. Ascorbic acid intake and plasma levels in healthy elderly people. *Am J Clin Nutr*. 1987;46:290–294.
25. Tallaksen CM, Bohmer T, Bell H. Concentrations of the water-soluble vitamins thiamin, ascorbic acid, and folic acid in serum and cerebrospinal fluid of healthy individuals. *Am J Clin Nutr*. 1992;56:559–564.

26. Barabas J, Nagy E, Degrell I. Ascorbic acid in cerebrospinal fluid-a possible protection against free radicals in the brain. *Arch Gerontol Geriatr*. 1995;21:43–48.
27. Brill S, Sedgwick PM, Hamann W, et al. Efficacy of intravenous magnesium in neuropathic pain. *Br J Anaesth*. 2002;89:711–714.
28. Gottrup H, Bach FW, Juhl G, et al. Differential effect of ketamine and lidocaine on spontaneous and mechanical evoked pain in patients with nerve injury pain. *Anesthesiology*. 2006;104:527–536.
29. Kim HK, Park SK, Zhou JL, et al. Reactive oxygen species (ROS) play an important role in a rat model of neuropathic pain. *Pain*. 2004;111:116–124.
30. Sweitzer SM, Hickey WF, Rutkowski MD, et al. Focal peripheral nerve injury induces leukocyte trafficking into the central nervous system: potential relationship to neuropathic pain. *Pain*. 2002;100:163–170.
31. Yoshimura M, Furue H. Mechanisms for the anti-nociceptive actions of the descending noradrenergic and serotonergic systems in the spinal cord. *J Pharmacol Sci*. 2006;101: 107–117.
32. Wu CM, Lin MW, Cheng JT, et al. Regulated, electroporation-mediated delivery of pro-opiomelanocortin gene suppresses chronic constriction injury-induced neuropathic pain in rats. *Gene Ther*. 2004;11:933–940.
33. Rice ME. Ascorbate regulation and its neuroprotective role in the brain. *Trends Neurosci*. 2000;23:209–216.
34. Lonnrot K, Metsa-Ketela T, Molnar G, et al. The effect of ascorbate and ubiquinone supplementation on plasma and CSF total antioxidant capacity. *Free Radic Biol Med*. 1996;21:211–217.
35. Gradl G, Gaida S, Finke B, et al. Exaggeration of tissue trauma induces signs and symptoms of acute CRPS I, however displays distinct differences to experimental CRPS II. *Neurosci Lett*. 2006;402:267–272.
36. Djouhri L, Koutsikou S, Fang X, et al. Spontaneous pain, both neuropathic and inflammatory, is related to frequency of spontaneous firing in intact C-fiber nociceptors. *J Neurosci*. 2006;26:1281–1292.
37. Rowbotham MC. Mechanisms of neuropathic pain and their implications for the design of clinical trials. *Neurology*. 2005; 65:S66–S73.

