The Vitamin C Controversy

To the Editor:

Recently, Chen et al[1] published an article in which they described 2 studies that were conducted. The title of this publication certainly draws the attention of the specialists who are involved in the treatment of patients with postherpetic neuralgia. This long-lasting, severe pain can have great consequences for the patient and his family. The quality of life is usually very poor.

The objective of the authors was to compare vitamin C between healthy volunteers and postherpetic neuralgia (PHN) patients (study 1) and they subsequently design a symptom-based and mechanism-based approach to assess the analgesic effect of intravenous vitamin C on spontaneous and brush-evoked pain (study 2). Study 1 was a cross-sectional study that enrolled 39 healthy volunteers and 38 PHN patients. According to the authors, this study showed that plasma concentrations of vitamin C were significantly lower in patients with PHN than in healthy volunteers. Study 2 showed that ascorbate treatment effectively restored plasma vitamin C concentrations in the patients, and decreased spontaneous pain [numeric rating pain scale (NRS) measurement) but not brush-evoked pain.

After carefully reading this study with much interest, I find that it contains many flaws, which raise a concern about, among others, the clinical significance of this study (in which they compiled 2 different studies in 1 article).

First, the authors mentioned that managing a PHN is a clinical challenge because of the variability in individual symptoms, treatment responses, and mechanisms. Often these symptoms converge in one patient, therefore in my opinion, it is useless to have a mechanism-based or symptom-based approach to these patients and then allow the selection of treatment.

In the first study, they recruited 38 patients with PHN with a persising pain lasting more than 3 months in the region of the cutaneous vesicular lesions from rash onset. Surprisingly, the authors did not mention the treatment these patients received before their first visit to the pain clinic. The authors evaluated the pain using the NRS scale for pain evaluation, and of course, the first measurement of NRS is dependent on which treatment these patients received initially, and how (un)successful these treatments were. In addition, the authors also mentioned some symptoms that the PHN patients had before the start of the study (poor appetite, insomnia, depression). These symptoms are also present in the common population, and therefore, also present in the control group. The authors did not mention this, therefore, this should raise serious concern about whether the groups are comparable while comparing the NRS scores. In addition, a poor appetite can influence vitamin C intake and subsequently cause lower plasma vitamin C levels, independent of whether the patient had PHN.

In the second study, the authors examined their hypothesis that vitamin C administration may help to relieve pain in PHN patients, and conducted a randomized, double-blinded, placebo-controlled intervention study. They mentioned that diagnoses ruled out other polyneuropathies, such as, compression fracture and spondylolisthesis. These last-mentioned diseases are of course no polyneuropathies and should raise a concern about the diagnostic criteria that these authors used in evaluating these patients. The authors surprisingly included only patients with spontaneous pain and not brush-evoked pain. After the inclusion of the patients in the study, they were asked whether they had brush-evoked pain. This is a big flaw in the study. The authors should have asked whether "brush-evoked pain" was already pre-existent. Therefore, it is of course not very surprising that spontaneous pain, and not brush-evoked pain, is influenced by vitamin C levels, which is one of the conclusions of the authors.

Furthermore, the primary efficacy measure was the change in the NRS score from day 1 to day 7. This period is much too short for drawing any conclusion with regard to clinical significance.

In addition, the authors mentioned that they had a washout period for certain medications, such as, benzodiazepines and anticonvulsants. At the start of the study, the authors did not conduct blood sampling measurements for these medications, therefore one could never say whether these medications were still present in the patient and could influence the NRS score. Furthermore, the authors were surprisingly not aware that suddenly stopping this medication can cause withdrawal symptoms, and can subsequently cause more pain. Patients were permitted to take rescue paracetamol, and in reading the article further, it remains unclear whether the patients were allowed to take paracetamol on a regular basis, which is different from taking rescue medication.

In addition, in study 2, patients were withdrawn from the study, but the data were included in the study. With regard to specimen collection, handling, and biochemical, determination, 2 different methods were used to measure vitamin C concentrations.

The same authors published a case report in 2006[2] in which they described only 1 patient with post herpetic neuralgia. This patient was treated with intravenous vitamin C daily on days 1, 3 and 5. After 1 week his intermittent, spontaneous, shooting pain had disappeared and he was advised to eat more fruits and vegetables (!). I think the authors designed their studies because of the results of this case report.

There are many pharmacological options possible for treating patients with postherpetic neuralgia. The most important are tricyclic antidepressive medications, antiepileptics, and opiates. There is scepsis with regard to the efficacy of treating patients with post-herpetic neuralgia with vitamin C. This study will not end this discussion. Until now, most of the research has been carried out in treating complex regional pain syndrome patients with vitamin C. More evidence is needed in good, placebo-controlled, randomized trials in PHN patients. Furthermore, a much longer follow-up is necessary. In conclusion, the authors wrote that patients with PHN may be highly susceptible to vitamin C deficiency, which may constitute a perpuating factor for chronic neuropathic pain, and may be a suitable adjuvant in multidrug treatment. This is very speculative of the authors and indicates the quality of this report. We, however, challenge the authors with designing new studies and to end the discussion on whether vitamin C is useful. It is a challenging topic, and we congratulate the authors that they are willing to resolve the controversy.

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

	Ascorbate Group		Placebo Group		
	N	Changes	N	Changes	*P*
Spontaneous pain	(21)	− (3.1 ± 1.6)	(20)	− (0.85 ± 1.09)	< 0.001
*Spontaneous pain	(20)	− (3.2 ± 1.5)	(19)	− (0.95 ± 1.03)	< 0.000
Brush-evoked pain	(21)	− (0.52 ± 0.75)	(20)	− (0.25 ± 0.55)	0.192
Brush-evoked pain					
+	(16)	− (0.73 ± 0.80)	(15)	− (0.33 ± 0.62)	0.171
−	(5)	0	(5)	0	
*+	(15)	− (0.69 ± 0.80)	(15)	− (0.33 ± 0.62)	0.129
*−	(5)	0	(4)	0	

*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).

Values (mean ± SD) between the 2 groups were analyzed using Mann-Whitney *U* test.

− indicates without brush-evoked pain before treatment; +, with brush-evoked pain before treatment; N, total number of patients; NRS, 11-point numeric rating pain scale (0-10); PHN, postherpetic neuralgia.

In Response:

We recently reported in the *Clin J Pain* that plasma vitamin C is lower in postherpetic neuralgia (PHN) patients, and the administration of vitamin C reduces spontaneous pain, but not brush-evoked pain.[1] We thank Drs Peek and van Zundert for their critical comments, even though they have not provided any references to support their points.

First and most critically, Drs Peek and van Zundert believed that "it is useless to have a mechanism-based or symptom-based approach in these patients, and then allow selection of treatment." In contrast to this opinion, many reviews[2–7] in the literature have advocated that the assessment of patterns of pain symptoms can identify the pathophysiological mechanisms, and can lead to mechanism-based treatment approaches to improve clinical management. Second, Drs Peek and van Zundert speculated that the controls in our study 1 may have had a poor appetite, which caused lower plasma vitamin C levels; hence, the low plasma vitamin C levels were independent of PHN. However, the average level of plasma vitamin C in our controls was 13.5 mg/L (median, 13.0), which is well within the normal range of the population (4.6 to 14.9 mg/L or 26.1 to 84.6 μmol/L).[8] In addition, their speculation is not supported by the observation that the plasma vitamin C level in our controls was much higher than that of our PHN patients. The plasma vitamin C level in PHN patients was 4.6 mg/dL (median, 3.1) in study 1, whereas the plasma vitamin C levels in the ascorbate group and the placebo group were 6.6 (median, 6.1) and 6.0 (median, 6.2), respectively, in study 2. Moreover, in agreement with our findings, a recent study, using a food-frequency questionnaire, attributes people with a higher risk for herpes zoster to a chronic lower fruit intake.[9] Indeed, vitamin C is primarily supplied by fruit intake because humans lack the ability to synthesize vitamin C.[10] Furthermore, our study 2—administration of vitamin C reduces spontaneous pain in PHN patients—provides strong support for the findings of study 1, by showing that a low plasma vitamin C level is one of the causes of PHN. Incidentally, we used the same method to measure vitamin C levels in both the studies, and not 2 different methods, as mistakenly stated by Drs Peek and van Zundert.

Drs Peek and van Zundert were correct to point out that we had failed to mention the treatment these patients had received before their first visit to the pain clinic. For the record, we state here that the patients that were included were either refractory to tricyclic antidepressants, anticonvulsants, and opiates, or unable to tolerate the side effects of these medications. Drs Peek and van Zundert also indicated that we should have asked if brush-evoked pain was already preexistent. In fact, we did. Thus, all patients that were included in study 2 had spontaneous pain, with or without, brush-evoked pain. As noted by Drs Peek and van Zundert, one patient in each group of study 2 withdrew from the study, but the data were included. To clarify the potential influence of these data, we have reanalyzed the results during this communication by excluding the data of the 2 withdrawn patients. As shown in Table 1, such exclusion of data does not significantly affect the outcome, that is, vitamin C treatment decreased spontaneous pain by 3.2 points, whereas the placebo group decreased by 0.95 points ($P < 0.0001$). For brush-evoked pain, vitamin C decreased the pain only by 0.69 points, which does not meet the criterion of a reduction of 2 points on 11-point numeric rating pain scale to suffice the improvement of pain.[11] As for the short duration of study 2, it is not uncommon for the duration of studies involving high-dosage intravenous vitamin C to be short. In fact, other investigators have used a duration of 1 week or a shorter period.[12,13]

As a final note, based on the many studies, which have shown that high concentrations of vitamin C preferentially decreased viral production in vitro,[14] Schenking et al hypothesized that vitamin C can decrease acute herpetic neuralgia (AHN), prevent the onset of PHN and reduce neuropathic pain in PHN.[15] In agreement with our findings, Schenking et al found that intravenous administration of high-dosage vitamin C, every other day for a week in 2 patients with AHN, improves Herpes zoster-induced efflorescence rapidly and decreases pain effectively.[15] Schenking et al are now conducting a large-scale clinical study based on these findings (personal communication). Furthermore, many studies[16–18] have shown that vitamin C decreases the prevalence of complex regional pain syndrome type I (CRPS I), a form of peripheral neuropathic pain syndrome. In sum we are optimistic that the results of the clinical trials will prove

