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Intravenous Vitamin C in the treatment of shingles: Results of a multicenter prospective cohort study

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Vitamin C is an immune-relevant micronutrient, which is depleted in viral infections and this deficiency seems to play a critical role in the pathogenesis of herpes infections and in the development of postherpetic neuralgia. The objective of this observational multicenter study was to evaluate the utilization, safety and efficacy of intravenously administrated vitamin C in patients with shingles.

Material/Methods: Between April 2009 and December 2010 16 general practitioners recorded data of 67 participants with symptomatic herpes zoster who received vitamin C intravenously (Pascorbin® 7.5 g/50 ml) for approximately 2 weeks in addition to standard treatment. The assessment of pain (VAS) and the dermatologic symptoms of shingles such as hemorrhagic lesions and the number of efflorescences were investigated in a follow-up observation phase of up to 12 weeks.

Results: Mean declines of pain scores (VAS), number of affected dermatomes and efflorescences, and the presence of hemorrhagic vesicles between the baseline and follow-up assessments at 2 and 12 weeks were statistically significant. Overall, 6.4% of the participants experienced post-herpetic neuralgia. Common complaints such as general fatigue and impaired concentration also improved during the study. The effects and the tolerability of the treatment were evaluated positively by the physicians. The risk of developing PHN was reduced.

Conclusions: The data presented here provide evidence that concomitant use of intravenously administered ascorbic acid may have beneficial effects on herpes zoster-associated pain, dermatologic findings and accompanying common complaints. To confirm our findings, randomized, placebo-controlled clinical studies are necessary.

key words: **shingles • postherpetic neuralgia • ascorbic acid**

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Background

Diagnosis and therapy of herpes zoster (HZ), characterized by dermatomal pain and vesicular rash, frequently involve consultations of general practitioners and hospitalization. Although there are several serious complications of zoster (ophthalmic, splanchnic, cerebral, motor complications), the most common and most feared one in immunocompetent adults is postherpetic neuralgia (PHN). Reported incidences of PHN range between 18% and 33% depending on patient age and assessment time after the infection [1–6]. A recent study reported that 24% of the patients studied had postherpetic neuralgia pain for more than 90 days after rash onset. Median duration of pain was 32.5 days and acute herpes zoster interfered in all health domains, especially sleep quality, enjoyment of life and general activities [1].

Because cellular immunity plays a critical role in reactivation and pathogenesis of *varicella zoster* virus infection [7], investigating the role of immune-relevant micronutrition is worthwhile from the therapeutic point of view. Vitamin C (ascorbate) is an essential nutrient. It is an important antioxidant [8] and co-factor of various enzymes and involved in the synthesis of collagen, carnitine, neurotransmitters and various neuropeptides and thus critically affects wound healing, energy metabolism, and nervous system function. The highest vitamin C levels are found in immune and nerve cells, reflecting the pivotal role of vitamin C in the function of these tissues [9–11].

Orally administered vitamin C leads to tightly controlled plasma concentration <0.02 mM. Pharmacologic plasma concentrations of vitamin C (>0.2 mM) can be achieved only by parenteral administration [12]. However, pharmacological concentrations are required for the beneficial effects on endothelial function [13], cellular immune function, antioxidative capacity [14], and pain relief [15].

As known from the literature, patients with viral infections exhibit vitamin C deficiencies [16]. This finding was recently confirmed in postherpetic neuralgia patients [17]. These deficient levels seem to play a critical role in the pathogenesis of herpes infections [18] and in the development of postherpetic neuralgia [19].

Low serum levels of vitamin C may be due to increased utilization of vitamin C for the detoxification of reactive oxygen species (ROS) during inflammation. Viral infections produce severe oxidative stress, contributing to cellular damage and disease progression. It was therefore proposed that in the clinical management of viral infections, especially in the early stages, considerable benefits should accrue from anti-oxidant repletion with dosages substantially above recommended daily allowances [20,21].

Studies evaluating the effects of Vitamin C in the treatment of herpes zoster are rare. Werbach compiled 2 experimental studies with intravenously administered 10 g vitamin C, finding beneficial effects on pain and dermatologic symptoms [22]. Such effects were also reported in case reports on herpes and postherpetic neuralgia patients after intravenous administration of vitamin C [23–26] and in a placebo-controlled pilot study [17]. However, there is an ongoing scientific debate on the therapeutic relevance of vitamin C in the treatment of herpes zoster [27].

The rationale of concomitant vitamin C use in acute herpetic and postherpetic neuralgia patients is to combat oxidative stress as a major contributing factor in the pathophysiology of inflammation, neurodegenerative/neuropsychiatric processes, inflammatory skin diseases, and pain [28].

The objective of the observational study presented here was to evaluate the utilization, safety and effects (in terms of reduction of infection-induced complaints) of intravenous (iv) vitamin C administration (Pascorbin® 7.5 g/50 ml) in patients with viral infections, especially shingles, in a primary care practice setting.

Material and Methods

Study objectives

Based on our recent investigations [24,25] we hypothesized that intravenously administered vitamin C exerts positive influences on the clinical outcome parameters of HZ, such as acute herpetic neuralgia (AHN) and PHN, and that it reduces dermatologic symptoms and number of affected dermatomes.

Study duration

This study was conducted from April 2009 to December 2010.

Study design

This multicenter, prospective cohort study (observational study) was performed by 16 general practitioners in Germany, who were experienced in the use of Complementary and Alternative Medicine (CAM) in the concomitant treatment of viral infections, especially shingles. The study design and concept, as well as its ethical validity and performance, were based on the actual recommendations of the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) (German Federal Institute for Drugs and Medical Devices) and the Paul Ehrlich Institute, in accordance with German laws and the principles of the Declaration of Helsinki and of Good Clinical Practice. The study was registered in Clinical Trials under the trial registration number NCT 00921934. Furthermore, this study followed the actual STROBE guidelines for items to be included in reports on observational studies [29].

Study setting

General practitioners recruited by an academic CAM study center received a briefing on the study protocol, the ethical and scientific basis of this observational study, the allocation procedure and the therapy schedule, before the start of the study, in accordance with the study protocol.

Data were collected before the start of vitamin C treatment (visit 1, baseline), after a clinical phase of approx 2 weeks (visit 2), and a follow-up observational phase of approximately a further 12 weeks (Figure 1).

Study participants

All elective patients of the primary care practices with symptomatic/acute herpes zoster infections were enrolled after

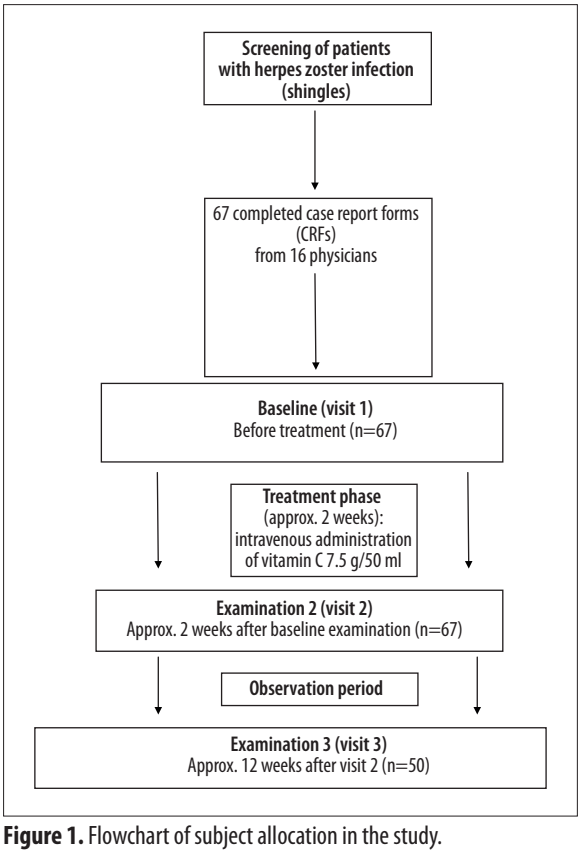

Figure 1. Flowchart of subject allocation in the study.

their informed written consent and a data privacy policy statement had been obtained. The patients were informed of possible adverse effects and the possibility to withdraw from the study at any time without any curtailment of their treatment. Inclusion and exclusion criteria are shown in (Figure 2). After the return of the completed case report forms (CRFs) it was evident that almost all patients studied had had symptomatic herpes zoster (67 out of 68). We therefore decided to focus this article on HZ but to retain the 1 patient without HZ in all baseline data (age, sex, body weight etc.) because her CRF was correctly completed according to the study design.

Variables studied

A. Primary outcome measures

The primary outcome measures were:

I. Pain intensity in patients with shingles during the whole study period was judged by the attending physician. Pain intensity was evaluated by means of a visual analogue scale (VAS) [*10-point visual analogue scale: 0 = no pain; 10 = very severe pain*]. Use, practicability, and validity of visual analogous scales are accepted in the scientific community and have been adequately evaluated [30,31].
II. The number of HZ-affected dermatomes was assessed at each visit by means of the following classification: 0 = none, 1 = 1, 2 = 2, 3 = >2.
III. Presence (or absence) of hemorrhagic vesicles in HZ patients was assessed at each visit. The numbers of subjects with hemorrhagic vesicles were compared between baseline and the follow-up visits.

Inclusion criteria

– Age >18
– Symptomatic herpes zoster (HZ) infection (shingles)
– Informed consent to participate in the observational study obtained

Exclusion criteria

– Age <18 years
History of:
– Oxalate-urolithiasis, nephrolithiasis
– Renal function impairment
– Iron storage disease (thalassemia, hämochromatosis, sideroblastic anaemia)
– Erythrocytic glucose-6-phosphate dehydrogenase deficiency
– Pregnancy and lactation
– Hypersensitivity to any of the ingredients

Figure 2. Eligibility criteria.

B. Secondary outcome measures

I. Number of efflorescences/vesicular lesions

Herpes zoster infection is usually associated with vesicular lesions. The number of vesicles was counted by the physicians at every visit throughout the whole study.

II. Efficacy assessment

At baseline, the efficacy of the previous medication(s) for the viral infection (if applicable) was assessed by means of the following rating scale:

- Good efficacy (symptoms were substantially improved);
- Moderate efficacy or no effect (symptoms were slightly improved, unchanged or worse).

III. Common symptoms – concentration impairment and general fatigue

At baseline visit 1 and visits 2 and 3 the physician evaluated the clinical symptoms and complaints of the patient (especially general symptoms such as general fatigue, concentration impairment, fever, and limb pain) by means of a 4-point Likert scale (not present, mild, moderate and strong). Only data of patients presenting the respective symptom at visit 1 and at least 1 other visit were included.

Interventions

In addition to the standard treatment including analgesics or virostatics at baseline, each patient received acorbic acid (Pascorbin® 7.5 g/50 ml) in 100 ml NaCL 0.9% as intravenous infusions (2–4 times/week) during the treatment phase of approximately 2 weeks.

Data sources/measurement

At each admission/visit, the patient's general condition and the disease-specific previous treatment/medication were recorded. At each medical examination, pain intensity (VAS) was measured. During the first admission the following data were collected and recorded: 1) the patient's clinical symptoms and complaints due to shingles; 2) location and number of the affected dermatomes; 3) number of single efflorescences; and 4) presence of hemorrhagic lesions.

Table 1. Schedule of data aquisition.

		Baseline/visit (1)	2 weeks after baseline (visit 2)	12 weeks after baseline (visit 3)
Assessment of demographic data	Age, gender, weight, height	X	–	–
Assessment of medication	Concomitant medication due to the inclusion diagnosis, general concomitant medication	X	–	–
Assessment of concomitant disease	Concomitant disease, immunosuppressive disease	X	–	–
Assessment of efficacy	Efficacy of the previous therapy	X	–	–
Assessment of symptoms	General symptoms (cough, runny nose, headache, limb pain, general fatigue, lack of concentration, body temperature)	X	X	X
	Dermatological symptoms (number of dermatomes, location of dermatomes, number of vesicles, hemorrhagic vesicles)	X	X	X
Assessment of pain	Visual analog scale	X	X	X
Assessment of drug changes	Drug changes (newly prescribed, withdrawn, dosage decreased, dosage increased)	–	X	X

At admission 2/visit 2 (approximately 2 weeks after the baseline visit) additional parameters (changes in medication and assessment of symptoms) were recorded.

At admission 3/visit 3, approximately 12 weeks after admission visit 1/baseline visit, the following parameters were assessed in addition to the clinical examination: 1) change of medication, 2) assessment of complaints, 3) assessment of vitamin C effects by patient and physician, and 4) possible adverse effects or side effects of vitamin C (Table 1).

Possible bias

Due to the study design, statistics were maintained only for the primary outcome parameters (VAS, number of affected dermatomes, and presence of hemorrhagic vesicles) and the assessment of efficacy.

Sample size

In total, 395 case report forms (CRFs) were issued to 63 therapists and 68 correctly and fully completed CRFs of patients with viral infections were returned by 16 general practitioners and were analyzed. In 67 of the 68 subjects, symptomatic herpes zoster was diagnosed.

Statistical methods

Assessment of pain

At each visit, pain was assessed by means of a 10-point visual analogue scale (VAS) ranging from 0 (=no pain) to 10 (= very severe pain). Changes from baseline were analyzed by means of the One-Sample t-test.

Number of afflicted dermatomes

At each visit, the number of afflicted dermatomes was assessed by means of the following classification: 0 = none, 1 = 1, 2 = 2, 3 = >2. The frequencies recorded at the baseline visit and the follow-up visits were compared by means of the (exact) Mantel-Haenszel test.

Presence of hemorrhagic vesicles

The presence (or absence) of hemorrhagic vesicles was compared between baseline and follow-up visits by means of Fisher's exact test.

Assessment of efficacy

At baseline, the efficacy of the previous viral infection medication (if applicable) was assessed by means of the following criteria:

- Good efficacy (symptoms were substantially improved);
- Moderate efficacy or no effect (symptoms were slightly improved, unchanged or worse).

The efficacy of ascorbic acid was evaluated and judged by the physician during and at the end of the observation period by means of the same criteria. The assessments of the efficacy of the previous applied viral infection medication and the following concomitant vitamin C therapy were compared by Fisher's exact test.

All data were checked for plausibility. The data were recorded in an ACCESS database (version 2007) using double data entry. After comparison of the data, they were exported to SPSS Version 19.0 and evaluated. In the context

of the descriptive data analysis, the following values were computed, depending on the type of parameter:

- For frequency data: absolute and relative frequencies;
- For proportionally scaled measured values: median, 25% and 75% quantiles, arithmetic mean, standard deviation, variance, minimum, maximum, number of valid data and number of missing data;
- Pre-/post-comparisons for the data concerning symptoms.

Allocation of the concomitant medication and the previous medication was conducted on the basis of the group classifications in the 2010 "Red List" [30]. Concomitant diseases were coded according to the ICD-10, German Modification, and classified according to the categories specified there. The focus was set on statistical tests for the main efficacy variables to investigate treatment effects occurring between baseline (visit 1) and the follow-up visits after 2 weeks (visit 2) and 12 weeks (visit 3). Patients could discontinue their participation after visit 2. Therefore, the changes between baseline visit and the last attended visit (visit 2 or visit 3) were also analyzed by applying the Last-Observation Carried Forward (LOCF) principle.

Results

Participants

In total, 395 case report forms (CRFs) were issued to 63 physicians and 68 correctly and fully CRFs were returned. Sixteen of the 63 initially interested physicians recorded the patient data completely and correctly. The participant rate of the selected physicians was 25.4%. The amount of fully completed CRFs was quite balanced throughout the participating primary care practices (10 physicians returned 5 CRFs each, 5 physicians returned 2, and 1 physician returned 8). Sixty-three (92.6%) patients had shingles, 4 patients had shingles combined with common cold or Epstein-Barr virus infection, and 1 patient had common cold only.

Descriptive Data

Overall, 42.6% of the participants were men (n=29) and 57.4% were women (n=39); the average age of the patients was 56.3 years (±20.4) and average BMI was 25.8 (±4.6). Thirty-one patients were enrolled immediately after the diagnosis of herpes zoster had been made (within 14 days), 30 patients had herpes zoster-associated complaints for 2 to 6 weeks, and the remaining 7 patients had zoster complaints for more than 6 weeks. The mean amount of vitamin C (in grams) per infusion/application was 9.9±4.6 g. On average, 8 infusions of ascorbic acid were given. At the start of treatment with ascorbic acid, 55.8% of the patients received medications related to the inclusion diagnosis, mainly antibiotics/anti-infectives (45.6%).

In 53 patients (77.9%) concomitant diseases were present; in total 191 diagnoses were reported (most frequently of the ICD group "Diseases of the circulatory system). Twenty-four patients had immunosuppressive disorders. Thirty-five patients (51.5%) used no medications for concomitant diseases; the remaining 33 patients (48.5%) received at least 1 medication (Table 2). At baseline, in the majority of patients the thoracic dermatomes were affected by shingles (43.9%), followed by the cervical (28.8%) and lumbar dermatomes (15.2%).

Table 2. Baseline patient characteristics.

Characteristics	Baseline/visit 1 (n=68*)
Age, y	
Total	56.30±20.4
Men	57.20±20.1
Women	55.50±20.8
Sex, n (%)	
Total	68
Men	29 (42.6%)
Women	39 (57.4%)
BMI, kg/m²	
Total	25.8±4.6
Men	27.6±4.9
Female	24.4±3.9
Weight, kg	
Total	73.1±14.3
Men	83.3±12.4
Women	65.6±10.6
Concomitant immunosuppressive disease**	
Yes	11 (16.2%)
No	57 (83.8%)
Duration of HZ-specific complaints (separated into groups)	
0 to 14 days	31 (45.6%)
2 to 6 weeks	30 (44.1%)
>6 weeks	7 (10.3%)
Number of concomitant medications for the inclusion diagnosis	
None	24 (35.3%)
1	24 (35.3%)
2	15 (22.1%)
3	2 (2.9%)
4	3 (4.4%)
Common symptoms at baseline general fatigue	
Not present	0 (0.0%)
Mild	30 (54.5%)
Moderate	20 (36.4%)
Strong	5 (9.1%)
Common symptoms at baseline impaired concentration	
Not present	0 (0.0%)
Mild	24 (54.5%)
Moderate	17 (38.6%)
Strong	3 (6.8%)

* 68 correctly and fully completed CRFs of patients with viral infections were returned, 67 of these patients had symptomatic herpes zoster.
** Immunosuppressive conditions = malignant neoformation of the mammae, diabetes mellitus, bronchial asthma, neurodermatitis, malignant neoformation, chemotherapy, breast ablation, hyperthyreosis, B-cell lymphoma, laryngeal cancer, pernicious anaemia, hepatitis, non-Hodgkin lymphoma, immunoglobulin-G deficiency, pneumoconiosis.

Table 3A. Assessment of pain (10-point VAS).

	V1 (baseline)	V2 (week 2)	V3 (week 12)	Last visit
N	64	64	47	64
Mean	5.8	2.2	0.6	1.2
Standard deviation	2.4	2.2	1.1	2.0
Median	6.0	2.0	0.0	0.2

Table 3B. Changes in assessment of pain (VAS) from baseline.

	V2 (week 2)	V3 (week 12)	Last visit
N	64	47	64
Mean	–3.7	–5.4	–4.7
Standard deviation	2.3	2.6	2.9
95% confidence interval	[–4.3; –3.1]	[–6.2; –4.7]	[–5.4; –4.0]
One-Sample t-test	p<0.0001	p<0.0001	p<0.0001

Table 4. Number of HZ-afflicted dermatomes.

	V1 (baseline)		V2 (week 2)		V3 (week 12)		Last visit	
	n	%	n	%	n	%	n	%
None	0	0.0	18	27.3	41	83.7	46	69.7
1	37	56.1	34	51.5	6	12.2	15	22.7
2	19	28.8	7	10.6	1	2.0	2	3.0
>2	10	15.2	7	10.6	1	2.0	3	4.5
Total	66	100.0	66	100.0	49	100.0	66	100.0
Mantel-Haenszel test, follow-up *vs.* baseline	–		p=0.0003		p<0.0001		p<0.0001	

Outcome data/main results

Pain: Three patients had no pain at baseline (score value = 0) and were thus excluded from the statistical analysis. The descriptive results per visit are presented in Table 3A. Fifty-nine patients (92.2%) showed an improvement of the VAS value; VAS scores deteriorated in only 1 patient, and 4 patients did not perceive any change in the sensation of pain. The mean VAS score decreases from baseline were statistically significant (p<0.0001) at all visits (Table 3B).

Number of HZ- affected dermatomes: One patient had no affected dermatomes at baseline and was thus excluded from the statistical analysis. At baseline, 29 patients (43.9%) presented with at least 2 affected dermatomes. At the end of the observation period, only in 5 patients there were still 2 or more affected dermatomes present, while almost 70% of the patients were free from herpes zoster lesions (Table 4). The reduction in number of affected dermatomes was statistically significant at all visits.

Presence (or absence) of hemorrhagic vesicles: At baseline, hemorrhagic vesicles were present in 32.8% of the patients; at follow-up only 2 patients (3%) had hemorrhagic vesicles; the improvement was statistically significant at all visits (Table 5).

Number of efflorescences/vesicular lesions

At visit 1/baseline, in the majority of the participants 1 to 30 vesicles were present. At the end of the observation period the majority of patients (57=86.4%) were free from vesicles (Table 6).

Assessment of efficacy

The efficacy of the ascorbic acid treatment was evaluated and judged by the physician during and at the end of the observation period. Only the 37 patients for whom an assessment of the previous medication was available were included in the analysis. Fisher's exact test yielded a significantly more positive rating for ascorbic acid treatment (Table 7).

Table 5. Presence of haemorrhagic vesicles.

	V1 (baseline)		V2 (week 2)		V3 (week 12)		Last visit	
	n	%	N	%	n	%	n	%
Yes	22	32.8	5	7.5	1	2.0	2	3.0
No	45	67.2	62	92.5	49	98.0	65	97.0
Total	67	100.0	67	100.0	50	100.0	67	100.0
Fisher's exact test, follow-up *vs.* baseline	–		p=0.0004		p<0.0001		p<0.0001	

Table 6. Number of efflorescences/vesicles.

Number of efflorescences	Visit 1		Visit 2		Visit 3		End of observation	
	n	%	n	%	n	%	n	%
No vesicle	0	0.0	29	43.9	47	94.0	57	86.4
1–30	44	66.7	32	48.5	2	4.0	8	12.1
31–70	14	21.2	3	4.5	0	0.0	0	0.0
More than 70	8	12.1	2	3.0	1	2.0	1	1.5
Valid data	66	100.0	66	100.0	50	100.0	66	100.0
Data missing	0	–	0	–	0	–	0	–

Table 7. Assessment of the efficacy of ascorbic acid *vs.* previous medication.

Efficacy rating	Previous		Ascorbic acid	
	n	%	n	%
Good efficacy	14	37.8	35	92.1
Moderate efficacy or no effect	23	62.2	3	7.9
Total	37	100.0	38	100.0
Fisher's exact test previous medication *vs.* ascorbic acid	P<0.0001			

Common symptoms - concentration impairment and general fatigue

At the beginning of the study, 20 patients (29.4%) had moderate or strong concentration impairment. At the end of the observation period, only 4 patients reported moderate or strong complaints and more than 68% patients showed no impairment of concentration (Table 8).

Twenty-five patients (45.5%) reported moderate or strong "general fatigue" at the beginning of the study. At visit 3, moderate complaints were still reported by 2 patients (5%). At the end of the observation period, 61.8% of the patients were free from these symptoms (Table 9). Overall, 78.2% (n=43) of the patients with general fatigue symptoms and 81.8% (n=36) of patients with impaired concentration improved during the whole course of the study (between baseline and the end of the observation period – Table 10).

Adverse effects were observed in 2 study subjects: 1 participant (aged 35 years) had itching and burning sensation on the injection site, followed by paraesthesia; another participant (aged 92 years) exhibited drug-induced urticaria, and according to the protocol the concomitant therapy with ascorbic was stopped. Both patients recovered without sequelae.

Discussion

In this multicenter observational study we observed beneficial effects of concomitant therapy with supraphysiological intravenous vitamin C doses in the treatment of herpes zoster. In the group of patients studied, the reduction of pain was significant in patients with herpes zoster (p<0.0001). In 59 patients (92.2%) an improvement of the VAS scores was achieved and the mean VAS decreases from baseline values were statistically significant at all visits (Table 3A, B). It

Table 8. Assessment of common symptoms: impaired concentration.

Impaired concentration	Visit 1		Visit 2		Visit 3		End of observation	
	n	%	n	%	n	%	n	%
Not present	0	0.0	25	56.8	24	77.4	30	68.2
Mild	24	54.5	15	34.1	5	16.1	10	22.7
Moderate	17	38.6	3	6.8	1	3.2	3	6.8
Strong	3	6.8	1	2.3	1	3.2	1	2.3
Valid data	44	100.0	44	100.0	31	100.0	44	100.0
Data missing	0	–	0	–	0	–	0	–

Table 9. Assessment of common symptoms: general fatigue.

General fatigue	Visit 1		Visit 2		Visit 3		End of observation	
	n	%	n	%	n	%	n	%
Not present	0	0	29	52.7	27	67.5	34	61.8
Mild	30	54.5	18	32.7	11	27.5	17	30.9
Moderate	20	36.4	7	12.7	2	5.0	3	5.5
Strong	5	9.1	1	1.8	0	0	1	1.8
Valid data	55	100.0	55	100.0	40	100.0	55	100.0
Data missing	0	–	0	–	0	–	0	–

Table 10. Changes of general symptoms, baseline/visit 1 *vs.* end of observation period.

Changes of symptoms	General fatigue		Impaired concentration	
	n	%	n	%
improved	43	78.2	36	81.8
unchanged	11	20.0	7	15.9
deteriorated	1	1.8	1	2.3

should be noted that 35.3% of the patients (n=24) received no other drug therapies for herpes zoster.

Because no control group was available in this observational study, we compared our results with the data from recent studies, with good comparability due to similar study design. Drolet et al, in a multicenter prospective study, evaluated the impact of herpes zoster and postherpetic neuralgia on health-related quality of life using a similar 10-point visual analogue scale [1].

Drolet et al specified postherpetic pain as pain persisting >90 days after rash onset.

The mean pain score at baseline in our study was 5.8, similar to the 6.3 mean score reported by Drolet. The subjects in Drolet's study reached a mean VAS score of 2.2 after 4 weeks of a standard therapy regimen including virostatics and analgesics; the subjects in our study reached a comparable pain reduction within a period of only of 2 weeks. After 90 days of standard treatment, Drolet demonstrated a >0.9 mean pain score, whereas in our ascorbic acid-treated study participants a pain score of 0.6 was achieved at the same time-point.

One of the most common and most feared complications of herpes zoster in immunocompetent adults is PHN, the definition of which is controversial. Drolet defined PHN as pain that was assigned a worst-pain score of ⩾3 and persisted for more than 90 days after rash onset. According to this differentiation of time periods, 24.1% of the subjects of the comparative study developed PHN, as compared to only 6.4% (3 participants) of our patients studied in the same period of time (findings at visit 3). It is therefore assumed that the

intravenous administration of vitamin C concomitant to the standard therapy of herpes zoster has significant effects on zoster-associated acute and subacute pain and might reduce the occurrence of PHN. These findings confirm the indications from previous case reports and pilot studies [17,24,25].

A typical zoster rash in immunocompetent individuals affects 1 or 2 adjacent dermatomes and usually lasts for 7–10 days. Thoracic dermatomes are most frequently affected [31]. In the affected dermatome, a relapsing and painful unilateral and asymmetrical erythema usually transforms into grouped vesicles within 12–24 hours. After another 2–4 days, swift confluence of these vesicles is observed and finally, approximately 7–12 days after rash onset, these vesicles are normally dried-out. In immunocompetent individuals, the zoster-specific vesicles and rash last until the resolution of the crusts, normally for 2–3 weeks [32]. At baseline, hemorrhagic lesions are found in approximately 16% of patients. The majority of patients develop less than 25 single efflorescences, 32% have 25–50 lesions, 10% develop 50–100 skin lesions, and 51–100 single efflorescences are found in only 2.7% of herpes zoster patients [33]. Comparing these dermatological data from the scientific literature with our results, we could also demonstrate that at baseline in the majority of our patients (84.9%) 1–2 dermatomes (84.9%) were affected, while in only a small proportion of patients (15.2%) were more than 3 dermatomes affected. Throughout our study we noticed statistically significant improvements and reductions in the number of affected dermatomes at all visits. Furthermore, the majority of our patients (43.9%) were affected by shingles of the thoracic region. In contrast to the literature data, more subjects (32.8%) in our study had hemorrhagic lesions at baseline (possibly due to the fact that 16.2% of subjects had immunosuppressive diseases), but the improvement of the hemorrhagic vesicles present was statistically significant at all visits. Regarding the number of single efflorescences, most of our study subjects (n=44, 66.7%) had 1 to 30 vesicles at visit 1/baseline. At the end of the treatment phase (visit 2), 43.9% of the subjects had no vesicles remaining, and at the end of the observation period the majority of patients (n=57, 86.4%) were symptom-free.

It is therefore evident from our study data that vitamin C application concomitant with standard therapy demonstrated a positive impact on the course of skin symptoms such as presence of hemorrhagic vesicles and number of single efflorescences in the dermatome during the course of shingles and that this combined therapy might achieve an early reduction of these symptoms.

Furthermore, common symptoms such as concentration impairment and general fatigue improved significantly throughout the study (Table 8–10). Similar results have been achieved in terminal cancer patients receiving 10 g vitamin C twice a day at intervals of 3 days. After 1 week, the symptom scores for fatigue and pain were significantly lower [15]. As evidenced by the literature, patients with viral infections, also confirmed for herpes zoster, exhibit vitamin C deficiencies [17], probably due to increased vitamin C utilization for ROS detoxification during infections. Restoring physiological vitamin C plasma concentrations by intravenous vitamin C administration may explain the strong protection effect against neuronal symptoms, since neuronal tissues are very vulnerable to oxidative stress. For example, vitamin C is highly concentrated in the brain and may thereby protect against ROS that accumulate during oxygen utilization.

Due to its significance for the immune and nerve systems, vitamin C deficiency during and after infections is probably a critical factor in risk of cellular immune and neuronal dysfunction contributing to reinfection, PHN, lack of concentration and fatigue.

In the present 68 patients, 2 non-serious and completely reversible adverse reactions were observed. The results of clinical studies confirm the safety of high-dose intravenous vitamin C (up to 1.5 g per kg body weight), keeping in mind the known and accepted contraindications such as oxalate calculus formation, renal failure, hemochromatosis, and glucose-6-phosphate dehydrogenase deficiency [34].

Strengths and weakness of the study

The major strength of our study was the combination of standard pain scores and the assessment of dermatologic symptoms such as the presence of hemorrhagic vesicles and number of efflorescences in the affected dermatome(s) during the study period. Furthermore, for the first time the combination of standard treatment of herpes zoster infection with supraphysiological-dosed intravenous vitamin C within the treatment phase was documented, and the treatment procedure was comparable to that of previous case studies [25]. The participating physicians were to record the numbers of efflorescences and to evaluate the presence of hemorrhagic vesicles at each visit, together with routine pain assessments (VAS). To our knowledge, no study using such a combined assessment of information on dermatological and pain symptoms has been previously published.

The major weakness of our study is the lack of a control group. Furthermore, the low response rate and the low number of patients may have biased the results. Another weakness of the study is that the clinical assessment of the herpes zoster infection without performing confirmatory diagnostic tests might have given rise to study bias, as was reported in other studies [35].

Conclusions

On the basis of our previous preclinical and clinical studies [24,25], and with respect to the fact that low concentrations of vitamin C (≤0.026 mM or 4,6 mg/l) were found to increase independently the PHN risk [17], the study presented here demonstrates that concomitant intravenous administration of ascorbic acid has positive effects on herpes zoster-associated pain and zoster-associated dermatologic findings. Furthermore, common clinical symptoms in patients with shingles, such as general fatigue and impaired concentration, were significantly improved and the risk of developing PHN was reduced.

To confirm our clinical findings, randomized placebo-controlled clinical studies are necessary.

Competing interests

MS and KK have declared that they have no competing interests. CV, GW, and JL are employed at Pascoe Pharmazeutische

Präparate GmbH (Giessen, Germany); AB and BG are employed at Dr. Loges + Co. GmbH (Winsen, Germany).

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REFERENCES:

1. Drolet M, Brisson M, Schmader KE et al: The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. Cmaj, 2010; 182(16): 1731–36
2. Tecklenburg SL, Mickleborough TD, Fly AD et al: Ascorbic acid supplementation attenuates exercise-induced bronchoconstriction in patients with asthma. Respir Med, 2007; 101(8): 1770–78
3. Czernichow S, Dupuy A, Flahault A, Chosidow O: [Herpes zoster: incidence study among "sentinel" general practitioners]. Ann Dermatol Venereol, 2001; 128(4): 497–501
4. Yawn BP, Saddier P, Wollan PC et al: A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc, 2007; 82(11): 1341–49
5. Scott FT, Leedham-Green ME, Barrett-Muir WY et al: A study of shingles and the development of postherpetic neuralgia in East London. J Med Virol, 2003; 70(Suppl.1): S24–30
6. Herr H: Prognostic factors of postherpetic neuralgia. J Korean Med Sci, 2002; 17(5): 655–59
7. Mueller NH, Gilden DH, Cohrs RJ et al: Varicella zoster virus infection: clinical features, molecular pathogenesis of disease, and latency. Neurol Clin, 2008; 26(3): 675–97, viii
8. Polidori MC, Mecocci P, Levine M, Frei B: Short-term and long-term vitamin C supplementation in humans dose-dependently increases the resistance of plasma to *ex vivo* lipid peroxidation. Arch Biochem Biophys, 2004; 423(1): 109–15
9. Moser U: Uptake of ascorbic acid by leukocytes. Ann N Y Acad Sci, 1987; 498: 200–15
10. Corti A, Casini AF, Pompella A: Cellular pathways for transport and efflux of ascorbate and dehydroascorbate. Arch Biochem Biophys, 2010; 500(2): 107–15
11. Rice ME, Russo-Menna I: Differential compartmentalization of brain ascorbate and glutathione between neurons and glia. Neuroscience, 1998; 82(4): 1213–23
12. Padayatty SJ, Sun H, Wang Y et al: Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med, 2004; 140(7): 533–37
13. Sherman DL, Keaney JF Jr, Biegelsen ES et al: Pharmacological concentrations of ascorbic acid are required for the beneficial effect on endothelial vasomotor function in hypertension. Hypertension, 2000; 35(4): 936–41
14. Du WD, Yuan ZR, Sun J et al: Therapeutic efficacy of high-dose vitamin C on acute pancreatitis and its potential mechanisms. World J Gastroenterol, 2003; 9(11): 2565–69
15. Yeom CH, Jung GC, Song KJ: Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration. J Korean Med Sci, 2007; 22(1): 7–11
16. Jain SK, Pemberton PW, Smith A et al: Oxidative stress in chronic hepatitis C: not just a feature of late stage disease. J Hepatol, 2002; 36(6): 805–11
17. Chen JY, Chang CY, Feng PH et al: Plasma vitamin C is lower in postherpetic neuralgia patients and administration of vitamin C reduces spontaneous pain but not brush-evoked pain. Clin J Pain, 2009; 25(7): 562–69
18. Terekhina NA, Petrovich Iu A, Batueva RA et al: [Lacrimal and salivary antioxidants in viral infection]. Klin Lab Diagn, 1998; (1): 13–15
19. Chen JY, Chu CC, Lin YS et al: Nutrient deficiencies as a risk factor in Taiwanese patients with postherpetic neuralgia. Br J Nutr, 2011; 106(5): 700–7
20. Stehbens WE: Oxidative stress in viral hepatitis and AIDS. Exp Mol Pathol, 2004; 77(2): 121–32
21. Okuda M, Li K, Beard MR, Showalter LA et al: Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. Gastroenterology, 2002; 122(2): 366–75
22. Werbach MR: Nutritional influences on illness: Herpes zoster. Keats Publishing, Inc. New Canaan, Connecticut: 216, 1987
23. Chen JY, Chu CC, So EC et al: Treatment of postherpetic neuralgia with intravenous administration of vitamin C. Anesth Analg, 2006; 103(6): 1616–17
24. Schencking M, Kraft K: Cantharidin patches and intravenous administration of vitamin C in the concomitant treatment of herpes zoster: a case report. Zhong Xi Yi Jie He Xue Bao, 2011; 9(4): 410–13
25. Schencking M, Sandholzer H, Frese T: Intravenous administration of vitamin C in the treatment of herpetic neuralgia: two case reports. Med Sci Monit, 2010; 16(5): CS58–61
26. Goldbaum JS: Vitamin C: the use of megascorbate therapy in general practice. A clinical experience. Australas Nurses J, 1982; 11(4): 20–21
27. Peek DF, van Zundert J: The vitamin C controversy. Clin J Pain, 2010; 26(6): 551–52; author reply 552–53
28. Johri N, Cooper B, Robertson W et al: An update and practical guide to renal stone management. Nephron Clin Pract, 2010; 116(3): c159–71
29. von Elm E, Altman DG, Egger M et al: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol, 2008; 61(4): 344–49
30. Rote Liste®. Rote Liste® Arzneimittelverzeichnis für Deutschland (einschließlich EU-Zulassungen und bestimmter Medizinprodukte) Rote Liste® Service GmbH, Frankfurt/Main, Germany, 2010
31. Boivin G, Jovey R, Elliott CT, Patrick DM: Management and prevention of herpes zoster: A Canadian perspective. Can J Infect Dis Med Microbiol, 2010; 21(1): 45–52
32. Gross G, Doerr HW: Herpes zoster guidelines of the German Dermatological Society. J Clin Virol, 2003; 27(3): 308–9
33. Wutzler PM, W. 94, Heft 17,25.April 1997(45) A-1129 [Herpes zoster – symptomatology. demographic data and prognostic factors]. Dt Ärzteblatt, 1997; 17: 1129
34. Hoffer LJ, Levine M, Assouline S et al: Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. Ann Oncol, 2008; 19(11): 1969–74
35. Helgason S, Petursson G, Gudmundsson S, Sigurdsson JA: Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. BMJ, 2000; 321(7264): 794–96