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Intravenous administration of vitamin C in the treatment of herpetic neuralgia: Two case reports

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Summary

Background: Acute herpetic neuralgia (AHN) due to a reactivated varicella zoster virus infection is a common problem. Furthermore, about 18% of all patients with confirmed herpes zoster (HZ) develop postherpetic neuralgia (PHN). The leading factors of the prognosis and persistence of symptoms are patient age and the size of the lesions. Animal studies came to a similar conclusions that in both AHN and PHN, inflammatory cytokines such as IL-6 and IL-8 could serve as predictive markers and that a positive influence of vitamin C administration, by modifying cytokine metabolism, could be demonstrated.

Case Report: Two patients (females aged 67 and 53 years) from an average and unselected patient group of a general practice with confirmed AHN were observed in the course of their illness. They received the basic analgesic (according to the WHO step scheme) and viral-static therapy. Furthermore, 15 g of vitamin C was administered intravenously every second day over a period of two weeks. Sudden and total remission of the neuropathic pain (measured on the basis of the visual analogous-scale, VAS) could be observed. Remission of the cutaneous lesions was noted within 10 days.

Conclusions: The use of the vitamin C appears to be an interesting component of alternative therapeutic strategies in the treatment of HZ. Especially for therapy-resistant cases of PHN, vitamin C administration should be examined as an additional option. To test and confirm the clinical findings, randomized clinical studies concerning the use of vitamin C in the concomitant treatment of zoster-associated neuralgia should be performed.

key words: **postherpetic neuralgia • Ascorbic Acid – immunology • immunodificiancy**

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BACKGROUND

The diagnosis and therapy of herpes zoster (HZ) is a frequent occurrence for the general practitioner and also in clinical circumstances. Although there are several serious complications of zoster (ophthalmic, splanchnic, cerebral, motor), the most common and feared in immunocompetent adults is postherpetic neuralgia (PHN). The definition of PHN is controversial. Recent data support the distinction between acute herpetic neuralgia (within 30 days of rash onset), sub-acute herpetic neuralgia (30–120 days after rash onset), and postherpetic neuralgia (pain lasting at least 120 days from rash onset) [1–3]. PHN is classed as neuropathic pain that is associated with mechanical allodynia, where normally innocuous tactile stimuli are perceived as painful [2].

In recent studies it is reported that the incidence of HZ is 3.2–4.1 in 1000 person-years [4,5]. At diagnosis of acute herpes zoster, 73% of patients received viral-static pharmacotherapy and 63% were treated with analgetics. 18.34% developed PHN [4]. The incidence of HZ and the accompanying complications increased with age. In another study, 18% of the adult patients with HZ were reported to suffer from a PHN as well. Furthermore, 33% of patients aged 79 years and older were affected with PHN [5]. Neuropathic pain, accompanied by nonspecific flu-like complaints, is known to be the most frequent symptom, with up to 81.6% in the early period of HZ. These main symptoms induced 22.8% of the patients to visit a doctor. At least 28.4% of the patients were affected by PHN, which therefore was determined as the most severe complication of HZ, with high advice and care expenditure [6]. Recently, the main points of interest are the average duration, prognostic factors, and the quality of life during herpetic neuralgia. A recent publication reports that 17% of patients with HZ still show a serious pain syndrome after 4 weeks and 11.7% reported the same pain intensity after 8 weeks. The leading factors of the prognosis and persistence of symptoms were the age of the patients and the size of the lesions [7].

Efficacy of therapeutic interventions

Hempenstall and coworkers [8] conducted a systematic review and meta-analysis of the efficacy and adverse events of analgesic PHN therapy between 1966 and 2004. They found 25 from-dear-pure publications referring to PHN. The success criterion was an improvement with the treatment of at least 50%. Oral medication with tricyclic antidepressants, tramadol, strong effective opiates, gabapentin, and pregabalin showed evidence of decreasing pain symptoms, but topical treatment with anesthetics and capsaicin also decreased pain. Another therapeutic option for severe cases are strong opiates. The use of N-methyl-D-aspartat glutamate receptor antagonists, for example memantine, was ineffective. Therapies with benzodiazepines, 5-HT_1-antagonists, aciclovir, intrathecal or epidural injection of lidocaine or cortisone, codeine, and non-steroidal anti-rheumatics (local or systemic) were also not associated with efficiency in PHN [8].

It followed from the meta-analyses that there are many severe and therapy-resistant cases which present therapeutic problems. Hopes of reducing it by varicella vaccination have recently receded. For this reason it is justified, for example for a general practitioner, to apply new therapeutic strategies with the approval of the patient. PHN requires the use of multi-modal pain-therapeutic interventions. The WHO step scheme has to be exhausted very often in general practice.

Experimental findings

It is undisputed that HZ is caused by the endogenous reactivation of varicella zoster virus (VZV), latent in ganglia cells after a primary infection, as a consequence of a decrease in specific varicella zoster viral immunity [9]. Therefore immune depression, immunosuppressive therapy, or immunogenic illness favoring an outbreak of HZ, for example HIV, diabetes mellitus, or cancer, may also be factors.

Because of lack of L-gulonolactone-oxidase activity, humans are not able to synthesize vitamin C. Therefore, intravenous or oral supplementation is necessary. It appears, however, that intravenous administration of vitamin C for therapeutic purposes is clearly superior to the oral route [10]. The use of intravenous vitamin C (ascorbic acid), which develops a protective function of proteins and lipids against oxygen free radicals to improve cellular immune function, has been investigated [11].

Cytokine activation and cytokines themselves were examined as possibly causing the progression of neuropathic pain in several recent studies. In an animal model of artificially induced neuropathic pain, elevated levels of TNF-α, interleukin-1β (IL-1β), and IL-6 have been demonstrated. On the other hand, significantly decreased levels of the anti-inflammatory IL-10 were found in the area of rat or mouse sciatic nerves (a model of chronic constriction injury). Furthermore, due to progression of PHN, an elevated level of IL-8 was verified as a marker and predictor of neuropathic pain [12]. IL-8 is known to be secreted by VZV-infected cells [13]. In another recent animal study concerning the influence of vitamin C on the production of TNF-α and IL-6 in ethyl-toxic liver disease it could be shown that in vitamin C-treated rats the serum concentration of TNF-α was considerably decreased compared with control groups. The serum concentration of IL-6 was also significantly ($p<0.001$) decreased. In this clinical context it was concluded that the levels of pro-inflammatory cytokines such as TNF-α and IL-6 could serve as predictive markers of progression in, for example, ethyl-toxic liver disease. TNF-α is also known to be an inductor of IL-8 synthesis [14].

Consequently, both animal studies came to the corresponding conclusion that in both PHN and in ethyl-toxic liver disease, inflammatory cytokines such as IL-6 and IL-8 could serve as predictive markers and a positive influence of vitamin C administration by modifying the cytokine metabolism could be demonstrated. The idea of an immune-modulatory and therapeutic effect of vitamin C raises the question of why the use of vitamin C in the treatment of HZ, AHN, and PHN has hardly been investigated [15].

Hypothesis

On the basis of the demonstrated production and release in experimental animal models of β-endorphins at hypothalamic neurons and the positive influence on neuropathic pain as well as the immune-modulating radical-scavenging,

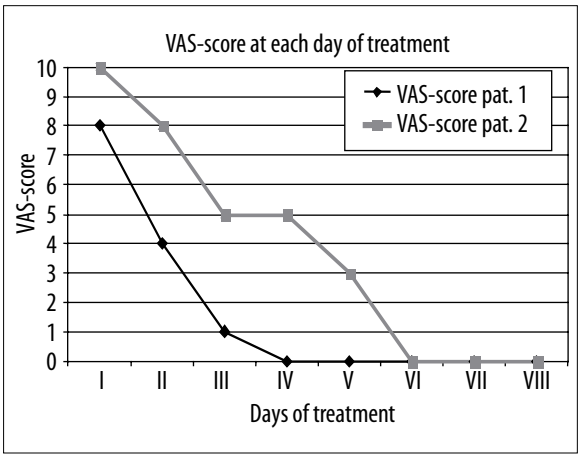

Figure 1. VAS – Score at each day of treatment. — and — represent vitamin C treatment (case 1 and 2); day 1 indicates the first day of treatment.

and selective cytotoxic effects of vitamin C, we hypothesize that vitamin C positively influences AHN, prevents the onset of PHN, and reduces the neuropathic pain occurring in PHN. We report two cases to illustrate our hypothesis.

Case Report

From the average and unselected patient group of a general-practice, two consecutive patients with acute HZ were selected who, accompanied by an evidence-based standard therapy regimen, were offered high-dose intravenous administration of vitamin C on the first day of diagnosis. A licensed formulation of ascorbic acid was used. It was administered at a dose of 15 g in 250 ml of physiological saline solution per session. The participation of the patients and the treatment followed the Declaration of Helsinki. Lack of glucose-6-phosphate-dehydrogenase, oxalate urolithiasis, iron storage disease, kidney insufficiency, and known oversensitivity reactions had been excluded before starting the therapy. Beside the clinical supervision of the therapy, the course of pain intensity was appraised on a 10-point Visual Analogous Scale (VAS: 0 – no pain, 10 – worst pain) and documented afterwards.

Case report 1

The first was a 67-year old female patient who had had hysterectomy and appendectomy, gravida II para II, with essential arterial hypertension (treated with the angiotensin II antagonist irbesartan) and slight hypercholesterolemia (ca. 6 mmol/l). The retired patient reported having a happy life without any stressors in the subjective prehistory. We saw a classic HZ affecting dermatome C1 with acute herpes right fronto-occipital in the forehead area at the hairline with classic unilateral skin rash without any affection of the right waiter-lid or eye. The rash had occurred the day before, complicated by an increasing right half-side headache, with the qualities of "burning, piercing, and booms". The initial intensity of her neuropathic pain on the VAS was 8 (Figure 1). The oral medication consisted initially of 125 mg brivudine per day for seven days and daily external application of a mixture of macrogol aryl ether and zinc oxide. On the wish of the patient she was offered only one single shot of analgesic with metamizole sodium (Novaminsulfon liquidum). The patient received repetitive infusions of 15 g of vitamin C. The compatibility of vitamin C was very good. A 40% reduction in rash with a tendency of end-desiccation and skin improvement was determined with the following infusion two days later. The patient reported a reduction of pain to a VAS-score of 4. Novaminsulfon was taken only one time during the night. The rash was reduced by ca. 80% at the third vitamin C infusion on the sixth day. The intensity of pain was described with a score of 1 on the VAS. The patient declared herself totally complaint free on the fourth date of infusion. Complete remission of the rash was noted. The infusion therapy was carried out two further times until the twelfth day of illness.

Case report 2

The second case was of a 53-year old patient for whom somatic and gynecological anamneses were inconspicuous and no prior intake of medications. Symptoms of a burn-out syndrome (insomnia and extended psychovegetative exhaustion), increased through constant professional stress, were noteworthy. A classic picture of acute HZ affecting dermatomes Th6/7 on the right became obvious. The skin rash reached from the dorsal to ventral and affected the whole submammary region. It occurred the day before, combined with a rapid increase in thoracic pain (VAS score: 10), which was described as "burning and piercing". The patient was overcome by strong distress pressure, completely dissolved, and cried. The oral medication was initially 125 mg brivudine per day for 7 days as well as daily external application of a mixture of macrogol aryl ether and zinc oxide. For effective pain management, the patient received 800 mg ibuprofen three times. Besides the "on-demand" medication of Novaminsulfon, the patient received gabapentin (300 mg on the first day, 600 mg on the second, and 900 mg afterwards in three single doses per day) because of the distinctive neuropathic pain. With the first consultation the patient received 15 g of vitamin C (repeated every second day). Compatibility was very good. Functional neural therapy of the involved dermatomes was repeated during every visit. A 20% reduction of the rash with end-desiccation tendency and skin improvement was determined on the following infusion date. The reported VAS score was 7–8 (Figure 1). Novaminsulfon was taken on demand two times. The initial appeared fraud under the gabapentin medication and an light nausea on the first day of taking brivudine had stopped. With the third vitamin C infusion on the sixth day, a decline of the rash by about 30% was determined. The pain intensity was at a VAS score of 5. The neuropathic pain changed its quality and was described as "dull". All rashes flattened out and minimized on the fifth day of infusion. The VAS score was 3. The analgesic medication was reduced. The patient was totally complaint free on the twelfth day of illness.

Discussion

The cases demonstrate a standard advice and treatment occasion of acute HZ with AHN in clinical practice. In these two patients who received intravenous administration of vitamin C we noted swift regression and clinical improvement of the HZ-induced rashes, rapid pain reduction illustrated by the VAS scores (Figure 1), and at least a prevention of a later ongoing PHN. The rapid therapeutic benefits in

these vitamin C-treated patients were impressive. In addition to an earlier investigation, there is only one publication which demonstrates the positive effects of vitamin C based on a case report concerning the therapy of PHN. The patient was treated with rather low-dosed vitamin C (2.5 g intravenously). Complete pain remission within one week was reached and it persisted for the whole observation time of at least three months [15]. Altogether, the above findings suggest a positive influence of vitamin C on both AHN and PHN. This is in accordance with the known facts about the pathogenesis of zoster-associated neuropathic pain and the described pharmacological effects of vitamin C. However, the latter has to be further elucidated.

Although this is a very small case series, the two patients were chosen from an unselected large number of patients in a general practice (completely without the background and design of an experimental study). Therefore, only a descriptive analysis of the experimental parameters of the two cases was carried out to demonstrate the significant changes in the clinical course. These two cases do not raise a claim of a clinical study according to CONSORT guidelines. The main limitation in our case series is that a comparison with a similar group of patients who did not receive the vitamin C treatment is missing.

Conclusions

To test and confirm our hypothesis, the development of clinical studies with high evidence power (for example double-blind, randomized, placebo-controlled) concerning the use of vitamin C in the treatment of zoster-associated neuralgia should be performed. The use of vitamin C appears to be an interesting component of alternative therapeutic strategies in the treatment of HZ. Especially in therapy-resistant cases of PHN, vitamin C administration should be examined as an additional option. On the basis of this study a prospective observational study was designed and evaluated [16].

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

References:

1. Baron R: Post-herpetic neuralgia case study: optimizing pain control. Eur J Neurol, 2004; 11(Suppl.1): 3–11
2. Dalziel RG, Bingham S, Sutton D et al: Allodynia in rats infected with varicella zoster virus – a small animal model for post-herpetic neuralgia. Brain Res Brain Res Rev, 2004; 46(2): 234–42
3. Sandholzer H: Postherpetische Neuralgie – eine Crux medicorum. Notfall & Hausarztmedizin (Notfallmedizin), 2005; 3: A437
4. Czernichow S, Dupuy A, Flahault A, Chosidow O: Herpes Zoster. incidence study among „sentinel" general practitioners. Ann Dermatol Venereol, 2001; 128(4): 497–501
5. 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
6. Wutzler P, Meister W: Herpes Zoster-Symptomatologie, demographische Daten und prognostische Faktoren: Ergebnisse einer prospektiven Studie an ambulanten Zosterpatienten in Deutschland. Dt Ärztebl, 1997; 94(17): A-1129/B-963/C-903
7. Herr H: Prognostic factors of postherpetic neuralgia. J Korean Med Sci, 2002; 17(5): 655–59
8. Hempenstall K, Nurmikko TJ, Johnson RW et al: Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med, 2005; 2(7): e164
9. Gross G, Schöfer H, Wassilew S et al: Herpes zoster guidelines of the German Dermatology Society (DDG). J Clin Virol, 2003; 26(3): 277–89, discussion 291–93
10. Nishikimi M, Koshizaka T, Ozawa T, Yagi K: Occurrence in humans and guinea pigs of the gene related to their missing enzyme L-gulonogamma-lactone oxidase. Arch Biochem Biophys, 1988; 267(2): 842–46
11. Davison G, Gleeson M: Influence of acute vitamin C and/or carbohydrate ingestion on hormonal, cytokine and immune responses to prolonged exercises. Int J Sport Nutr Exerc Metab, 2005; 15(5): 465–79
12. Schäfers M, Sommer C: Anticytokine therapy in neuropathic pain management. Expert Rev Neurother, 2007; 7(11): 1613–27
13. Desloges N, Schubert C, Wolff MH, Rahaus M: Varicella-zoster virus infection induces the secretion of interleukin-8. Med Microbiol Immunol, 2008; 197(3): 277–84
14. El-Taukhy MA, Salama SM, Abou-Shousha SA et al: Effects of chronic ethanol and vitamin C administration on production of tumor necrosis factor-alpha and interleukin-6 in rats. Egypt J Immunol, 2006; 13(1): 1–10
15. Chen JY, Chu CC, So EC et al: Treatment of postherpetic neuralgia with intravenous administration of vitamin C. Anaest Analg, 2006; 103(6): 1616–17
16. Clinical Trials: NCT 00921934 (*http://clinicaltrials.gov/ct2/show/NCT00921934?term=zoster+vitamin+c&rank=1*)