Cantharidin patches and intravenous administration of vitamin C in the concomitant treatment of herpes zoster: a case report

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The diagnosis and therapy for herpes zoster (HZ) are frequently associated with consultation of a general practitioner and with hospital care. Although there are several serious complications of zoster such as ophthalmic, splanchnic, cerebrum, and motor conditions, the most common and feared in immunocompetent adults is postherpetic neuralgia (PHN). Its definition is controversial. Recent data support the distinction between acute herpetic neuralgia (within 30 d of rash onset), subacute herpetic neuralgia (30 to 120 d after rash onset), and postherpetic neuralgia (defined as pain lasting at least 120 d from rash onset)1-3. PHN is classified as a neuropathic pain that is associated with mechanical allodynia where normally innocuous tactile stimuli are perceived as painful4. In actual studies it is reported that the incidence of HZ is 3.2 to 4.1 in 1 000 person-years5-8. At diagnosis of acute HZ, 73% of the patients received a virus static pharmacotherapy, 63% were treated with analgesics and 18.34% developed a PHN9. The incidence of HZ and the accompanying complications increased with age. In another study, 18% of the adult patients with HZ were reported to also suffer from PHN. Furthermore, 33% of patients aged 79 years and older were affected by PHN10. Neuropathic pain, accompanied by a non-specific flu-like disorder, is known to be the most frequent symptom appearing in up to 81.6% of patients in the early stages 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 was therefore found to be the most severe complication of HZ with high expenditure on advice and care11. In recent studies, the main points of interest were the average duration, the prognostic factors and the quality of life associated with herpetic neuralgia: a recent publication reported that 17% of patients with HZ still had severe pain after 4 weeks, and 11.7% reported the same pain intensity after 8 weeks12.

Hempenstall et al13 conducted a systematic review and meta-analysis of the efficacy and adverse events of analgesic PHN therapy between 1966 and 2004. They found 25 publications referring to PHN. Success criterion was an improvement
following treatment of at least 50%. Oral medication with tricyclic antidepressants, tramadol, opiates, gabapentin and pregabalin showed evidence of decreasing pain symptoms. In addition, topical treatment with anaesthetics and capsaicin decreased the pain.

It remains undisputed that HZ is caused by an endogenous reactivation (after the primary infection existing latently in the ganglia cells) of the varicella zoster virus (VZV) as a consequence of a decrease in specific varicella zoster virus immunity[24]. Consequently an immune depression, immunosuppressive therapy or immunogenenic illness could favour the outbreak of HZ, as in HIV, diabetes mellitus or cancer. Due to the waning of T cell immunity in the virus in later life, advanced age is the most significant risk factor for the occurrence of reactivated HZ. Therefore, most cases occur in older patients in studies[25]. Due to a lack of L-gulonolactone oxidase activity, humans are not able to synthesize vitamin C. Therefore, an intravenous or oral supplementation is necessary. On this occasion, however, it became apparent that the intravenous administration of vitamin C for therapeutic purposes is clearly superior to oral administration[26].

Vitamin C (ascorbic acid) develops a protection function of proteins and lipids against free oxygen-radicals to improve cellular immune function[27]. Cytokine activation and cytokines themselves were examined as possibly causing the progression of neuropathic pain in a recent paper. In the animal model of artificially induced neuropathic pain, elevated levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6 have been proved and demonstrated. On the other hand, significantly decreased levels of anti-inflammatory IL-10 were found in the area of rats or mice sciatic nerves (model of chronic constriction injury). Furthermore and due to a progression of PHN, an elevated level of IL-8 was verified as a marker and predictor of neuropathic pain[28]. IL-8 is known to be secreted by VZV-infected cells[29].

In another recent animal-experimental paper concerning the administration and influence of vitamin C on the production of TNF-α and IL-6 in ethyl-toxic liver disease, it showed that in rats treated with vitamin C, the serum concentration of TNF-α was considerably decreased in comparison to that in the control groups. The serum-concentration of IL-6 was also significantly (P<0.001) decreased. In this clinical context, it was concluded that levels of pro-inflammatory cytokines, such as TNF-α and IL-6, could serve as predictive markers of progression in ethyl-toxic liver disease. TNF-α is also known to be an inducer of IL-8 synthesis[30].

As a consequence, both animal-experimental works came to the corresponding conclusion that as well as with the PHN and in the 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.

Cantharidin treatment is based on the use of cantharidin (a poisonous compound secreted by the Spanish fly) which, as a so-called “vesicant”, induces a local grade I or II burn effect with the formation of a patch at the application site due to histaminergic constituents. This precipitates an immunological effect with unspecific activation of T and B lymphocytes and plasma cells with the release of immunoglobulins, prostaglandins and leukotrienes with reactive local inflow of other substances including β-endorphins. This forms the basis of its use as adjunct therapy for neuropathic or radicular pain[31].

1 Case report

A 65-year-old male patient was hospitalised for cardiological rehabilitation after coronary intervention for a 90% medial stenosis of the right coronary artery (percutaneous transluminal coronary angioplasty and implantation of a 2.75/18 Promus stent). The cardiovascular risk factors were mixed hyperlipidaemia, arterial hypertension, and 20 plus years of smoking. Cardiologically he was in compensated heart failure, New York Heart Association class II, with hypertensive heart disease and mitral and aortic regurgitation. Previous medication consisted of 5 mg bisoprolol daily, 5 mg amiodipine daily, 40 mg atorvastatin daily, 100 mg acetylsaliclic acid daily, and 75 mg clopidogrel daily. At admission his cardiopulmonary and skin findings were unremarkable although the patient did report itchy skin over the D4 dermatome on the right.

The day after admission, the patient already presented with painful skin findings in the right axilla (Figures 1A and 1B), which was diagnosed as extensive HZ of dermatomes T4 to T6 with multiple haemorrhagic pustulous efflorescences. The pain sensations in the affected dermatomes were described as severe with the qualities “stabbing and burning”. The patient classified his pain with a score of 8 on a 10-point numerical analogue scale (NAS) (0 = no pain, 10 = most severe pain imaginable).

![Figure 1](image1.png)  
**Figure 1** Manifestation before treatment

The day after admission, the patient already presented with painful skin findings in the right axilla.
In addition to standardised virostatic disease-modifying therapy with oral administration of 125 mg brivudine daily, topical polidocanol ointment (twice daily) and 1 500 mg metamizole daily (3×500 mg per oral) for 7 consecutive days; the patient was also given intravenous injection of 7.5 g ascorbic acid every second day for 2 weeks. In addition, cantharidin patches were applied below the affected dermatome 3 times a week (3 to 4 plasters sized 1×1 cm) for 2 weeks. During the first 2 weeks, a 50% reduction in pain was measured on the NAS scale and a significant reduction of the haemorrhagic skin efflorescences was documented (Figure 2).

![Figure 2](image)

*Figure 2  Treatment with cantharidin patches for 2 weeks*
During the first 2 weeks, a significant reduction of the haemorrhagic skin efflorescences was documented

In the last week of inpatient treatment, there were only minimal isolated efflorescences and the neuropathic pain was barely perceivable for the patient. The tolerability of the cantharidin patch and the medication, including vitamin C, was described as very good; no undesirable effects or side effects were observed. When the patient was asked by telephone 8 weeks later, he reported that he was still completely pain-free and the skin over the affected dermatomes was unremarkable.

2 Discussion

The case demonstrates a standard advice and treatment scenario of acute HZ with acute herpetic neuralgia (AHN) in clinical practice. In the patient who received the intravenous administration of vitamin C and cantharidin patches beside standard analgesic and virostatic treatment, a swift regression and clinical improvement of the HZ-induced efflorescences was obtained, rapid pain reduction was illustrated by the NAS-scores and possibly of prevention of a later ongoing PHN were presented. The rapid therapy benefits were impressive.

Adjacent to an earlier investigation, only two publications existed, demonstrating the positive effects of vitamin C based on a case report and a cross-sectional study concerning the therapy of PHN\textsuperscript{[10, 11]} In the case report the patient was treated with rather low-dose vitamin C (2.5 g intravenously). Complete pain-remission within one week was reached. It persisted throughout the observation time of at least 3 months\textsuperscript{[11]}. In another cross-sectional study, it became obvious that plasma-vitamin C levels were significantly lower in patients with PHN than in healthy volunteers. Furthermore, ascorbate treatment effectively decreased spontaneous pain in patients with PHN\textsuperscript{[11]}. Shingles (HZ infection) have been successfully treated with antioxidative substances like high-dose vitamin C for some time. Not only can the acute symptoms be diminished by high-dose vitamin C, even long-term sequelae, like painful post-herpetic neuropathy, may be mitigated or even fully avoided. Nevertheless, there is a remaining sceptis with regard to the efficacy of treating patients with PHN with vitamin C because of a lack of evidence (a lack of well-designed, placebo-controlled, randomized trials in PHN patients)\textsuperscript{[10]}. Basis of the effects of cantharidin patches in the concomitant treatment of neuropathic pain syndromes such as complex regional pain syndrome and PHN is (1) the immune-modulating effect of cantharidin with a non-specific activation of T and B lymphocytes, and (2) a non-specific release of plasma-cells, prostaglandins and leukotriene, followed by a reactive inflow of β-endorphins\textsuperscript{[11]}. However, this case report does not enable differentiation as to which of the treatments were responsible for the clinical improvement.

Altogether, the above-mentioned findings suggest a positive influence of vitamin C and cantharidin patches on AHN. 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.

3 Conclusion

To test and confirm the hypothesis, well designed clinical studies (double-blind, randomized, placebo-controlled, cross-over, for example) should be performed on the use of vitamin C in the treatment of zoster-associated neuralgia. An observational cohort study was conducted to test the hypothesis, including adult patients suffering from acute viral infection, especially HZ, presenting themselves in primary care centers or hospitals all over Germany, and who are treated with standard therapy and add-on vitamin C (closing date 2011)\textsuperscript{[11]}.

The use of vitamin C and cantharidin patches appears to be an interesting component of alternative therapeutic strategies in the concomitant treatment of HZ. Especially for therapy-resistant cases of AHN and PHN, vitamin C and cantharidin blister administration should be examined as an additional option.

4 Consent

Written informed consent was obtained from the patient for publication of this case report and
accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

5 Competing interests

The authors declare that they have no competing interests.

6 Authors’ contributions

MS wrote the presentation of the case report and contributed to the discussion section. Furthermore, he researched the patient information and was a major contributor to the presentation section of the manuscript. MS and KK researched the literature review on vitamin C and contributed to the discussion section. KK edited and revised the entire manuscript and was a major contributor to the discussion section. All the authors read and approved the final manuscript.

REFERENCES


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关键词：疱疹；带状；斑蝥素；抗坏血酸；病例报告