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Argon Laser Induced Cutaneous Sensory and Pain Thresholds in Post-herpetic Neuralgia. Quantitative Modulation by Topical Capsaicin

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Sensory and pain thresholds to cutaneous argon laser stimulation were determined in patients with post-herpetic neuralgia before and during treatment with topical capsaicin. Before treatment both thresholds were significantly elevated on the affected side compared to the contralateral normal area. After one week of capsaicin treatment both thresholds were significantly increased compared to the pre-treatment values, and the subjective pain relief, measured on a visual analogue scale (VAS) was 24%. More than 10% decrease in VAS pain score was obtained by 62.5% of the patients. Laser stimulations at levels at which the sensory and pain thresholds are reached were initially described as burning or stinging with pain projecting outside the stimulated area. This allodynia to laser stimulations changed during capsaicin treatment towards normal sensory and pain perception qualities. Both sensory and pain thresholds and the subjective pain score evaluated on a visual analogue scale were attenuated during the capsaicin treatment, suggesting a significant role of the cutaneous sensory and pain receptors in postherpetic neuralgia. ***Key words: Anaestesia; Analgesia; Pain.***

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Herpes zoster is a chronic infection by varicella zoster virus. Especially in elderly persons, the acute neurocutaneous symptoms may be followed by neuralgia lasting more than 3 months after healing of the acute lesions. This postherpetic neuralgia (PHN), may be extremely painful and may result in depressions and even suicide. Reviews of PHN reveal no effective treatment modality (1, 2, 3), but Bernstein et al. (4) reported that topical capsaicin produced substantial pain relief in 75% of the patients treated, whereas Watson et al. (5) found that only 39% achieved a good result. The mechanism behind the effect of capsaicin treatment of PHN is not clear. Capsaicin (trans-8-methyl-vanillyl-6-nonenamide) is the pungent substance in hot peppers, and has since 1850 been used as a treatment for toothache (6). Sensory nerves, containing Substance P (SP) and presumably other neuropeptides as peripheral transmitters have been shown to be involved in the perception of cutaneous pain (7–12). These neurons are susceptible to peripheral neurotransmitter depletion after topical capsaicin treatment (13, 14), which modulates the response characteristics. In normal skin, the nerves are initially stimulated by the release of peripheral neurotransmitters, but after prolonged treatment, the depletion of transmitters renders the skin anaesthetized.

The aim of the present study was to investigate peripheral mechanisms behind PHN, especially why capasaicin in some cases, as described in the literature, can alleviate the pain in PHN. The study showed that, in spite of initial subjective discomfort, topical capsaicin treatment may be useful for patients with PHN, in which no other medication is effective.

MATERIALS AND METHODS

Patients

Eight patients, mean age 74.3 years (64 to 82), 3 males and 5 females who were referred to the outpatient clinic were included. The median duration of PHN was 36 months. All were concomitantly treated by their usual medications in their usual dosages, which for all patients was insufficient for relieving the pain. The drugs included acetaminophene, aspirin, codeine, benzodiazepins, carbamazepin, phenothiazins, amitriptylin and morphine analogues. The lesions were all unilateral, and located on thoracic dermatomes in 5 patients, on the head (C1 dermatome) in 1 patient, and on the lower extremity (S1) in one patient. The study was approved by the local Ethical Committee, and followed the recommendations of the Helsinki Declaration.

Capsaicin treatment

Capsaicin (Sigma, USA) was dissolved in ethanol and mixed with a moisturizing cream to a final concentration of 0.1 mg/ml. A blinded, placebo controlled scheme of application was intended, but due to elicitation of a sensation of warmth and burning at the initial capsaicin applications, the capsaicin cream could always be recognized by the patients. The cream was applied 5 times daily on the affected area for 5 weeks.

Monitoring of sensory and pain thresholds

Sensory- and pain thresholds were determined before, and after 1, 3 and 5 weeks of treatment. The laser energy was delivered to the skin by a quartz fibre, and the beam diameter on the skin surface was 3 mm. The argon laser pulses had a duration of 200 ms (Lexel Aurora 150, USA). Before treatment, a skin area of approximately 10 cm^2 on the affected skin area was marked with a pen, and the symmetrical area on the normal side served as a control. During the study, all measurements were performed inside these areas. Here, the sensory thresholds were determined as the lowest laser energy, which could be percived at all. Under normal circumstances, this is a warmth sensation. Pain threshold was defined as the minimal laser energy, which could elicit a distinct, sharp pinprick sensation without warmth or any burning after-sensation. The thresholds were determined as previously described by Arendt-Nielsen & Bjerring (15).

Subjective pain score

The pain intensity (regardless of the type of pain and medication) was scored daily on a 10 cm visual analogue scale marked 'no pain' at one end and 'maximal pain' at the other. Later, the pre-treatment score was normalized to 100%, and the daily pain ratings were calculated in relation to this value.

Statistics

For statistical anlysis the Wilcoxon's test was used. $p<0.05$ was considered significant.

RESULTS

Subjective effect of capsaicin treatment

Initially, a discomforting feeling of warmth, and even a burning feeling immediately after application of the cream was reported by all patients, but after 3–6 days only a few complaints were reported. The subjective effect of capsaicin treatment was found important only if the pain reduction exceeded 10% on a visual analogue scale compared to the initial score. Pain relief was reported by 62.5% of the patients after the first week. The mean reduction of pain intensity was 24% (Fig. 1). The patients who responded to the treatment did not improve further after the first week, and those who did not respond to the treatment after the first week, remained non-responders.

None of the patients reported increased pain during the treatment, and in no case did the visual analogue scale score increase during treatment. After the study was completed, only 3 patients wished to continue the capsaicin treatment, and one month later, none of the participants used the capsaicin cream.

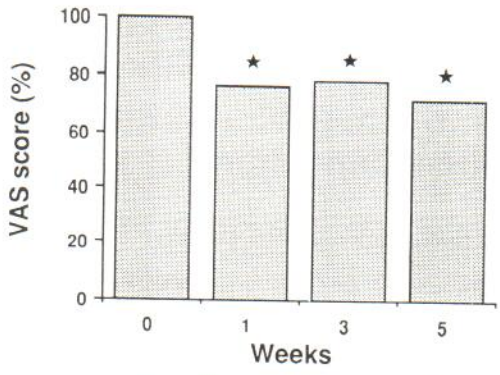

Fig. 1. The effect of topical capsaicin applied 5 times daily for 5 weeks. The subjective pain relief was rated on a visual analogue scale (VAS), and the mean of one week's initial score before treatment was given the value of 100%. Asterisks indicate significant ($p<0.05$) pain relief for the eight patients compared to pre-treatment ratings.

Laser induced sensory and pain thresholds on normal and affected skin before treatment

On the affected side the sensory threshold was elevated significantly ($p<0.05$) before treatment (Fig. 2A) compared to the normal contralateral side. The sensory threshold to argon laser stimulation is normally reported as a warmth sensation. All patients, however, reacted strongly to laser stimulations at the level of the sensory threshold, and described the feeling as a long lasting unpleasant burning pain. The pain threshold was also significantly elevated ($p<0.05$) on the affected side before treatment (Fig. 2B), and again the patients found laser stimulation of an intensity just at the pain threshold level more stinging and painful on the affected side. The pain was described as a sharp, spreading and stinging pain, in quality similar to their postherpetic neuralgia, but mostly of shorter duration.

Laser induced sensory and pain thresholds after capsaicin treatment

The sensory and pain thresholds were significantly increased after 1 week of capsaicin treatment compared to the initial values (Fig. 2). The thresholds measured 3 and 5 weeks after onset of treatment were not significantly different from the 1 week values.

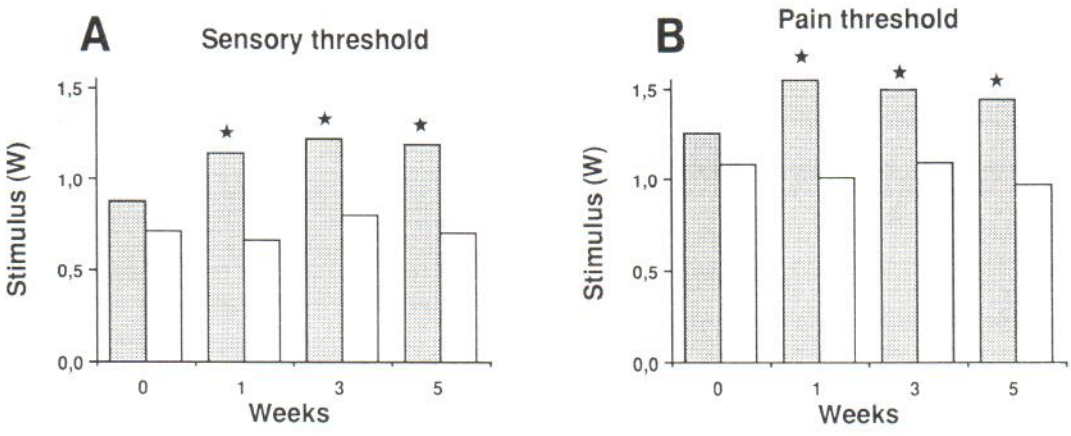

Fig. 2. The sensory (A) and pain (B) thresholds to cutaneous argon laser stimulations on the affected (hatched) and normal (blank) side. Before capsaicin treatment, the thresholds were elevated on the PHN affected areas. During treatment of the affected side the thresholds increased significantly compared to the initial values. Asterisks indicate significant ($p<0.05$) increased thresholds compared to pre-treatment values.

The burning perception after laser stimulation at the sensory threshold and the neuralgia-like stinging pain at the pain threshold were both reduced in intensity. At the end of the treatment period, laser stimulations at both sensory and pain threshold levels were reported as less unpleasant than before treatment, and the reduction in intensity of the unpleasant feeling after stimulation at the thresholds corresponded to the subjective effects of topical capsaicin on postherpetic neuralgia, as scored by the patients on a visual analogue scale.

DISCUSSION

Subjective effect of capsaicin on postherpetic neuralgia

In the study of Bernstein et al. (4) topical application of capsaicin improved the subjective status in up to 75% of PHN patients (12 patients: 3 completely pain free, 2 much better, 3 better), whereas Watson et al. (6) found more moderate effects: 39% of the patients had at least good results and 53% were improved or better after 4 weeks of capsaicin treatment (verbal intensity scale). In the present study 62% of the patients reported a moderate relief (24% reduction of the pain score on a visual analogue scale). The variation in pain reduction in the different studies may be ascribed to different treatment schedules. Bernstein et al. used capsaicin 0.025% 5 times a day for 1 week and then three times daily for additional 3 weeks. Watson et al. also used capsaicin 0.025%, but applied the cream four times daily.

Laser induced sensory and pain thresholds on normal and affected skin

Dyck et al. (16) suggested that pain associated with neuropathies might be related to the rate of degeneration of the small diameter afferent fibres (A δ and C-fibres). Degenerations of the peripheral nerve fibres may induce an abnormal central modulation and perpetuation of pain—a theory, which is supported by the initial findings of allodynia at laser intensities at levels approximately at sensory and pain thresholds. Similar qualitative alterations of sensory and pain perceptions in PHN were also reported in the study of Nurmikko et al. (17).

Laser induced sensory and pain thresholds during capsaicin treatment

In the present study, a quantification of the function of the thin cutaneous afferent nerve fibres was performed before and during 5 weeks of topical capsaicin applied 5 times a day. Watson et al. (5) found increasing effect of the topical capsaicin applications during 4 weeks of treatment, and they stressed the necessity of frequent application (4 times a day). In the present study, the significant effect was observed after only 1 week, and no further increase in effect was seen during the 4 following weeks of treatment.

Compared to a previous study of the dynamics of sensory- and pain thresholds during long-term capsa-

icin treatment the increase of sensory and pain thresholds during topical capsaicin treatment of PHN skin is within the normal range during the first week (18). Hereafter, the effect was declining, and total analgesia was not obtained in the PHN affected skin.

Long-term topical capsaicin treatment depletes SP and other neurotransmitters from the peripheral nerve terminals. The physiological release of SP into the perineural space upon nerve excitation is exhausted and the neurogenic component of inflammation is inhibited (19, 20). A central defect in the spinal modulation of peripheral sensory signals may be present in PHN as suggested by Noordenbos (21), who found that the pain in PHN was due to loss of large (inhibitory) fibres with intact small (excitatory) fibres, but immunohistological studies of nerve roots obtained by autopsy (22), showed substance P staining in a case, in which PHN had lasted for 5 years. Also histological studies have identified fibrosis of both peripheral nerves (23) and nerve roots in PHN (22). Jancsó et al. (24) demonstrated impairment of the axon reflex vasodilatation after herpes zoster. In our patients, however, the distal afferent nerve fibres apparently were operational during the capsaicin treatment as the argon laser stimulations were perceived as warmth and pain—but at laser energy levels higher than on the normal skin.

CONCLUSION

Quantification of sensory and pain threshold by laser stimulation of normal skin and skin affected with PHN initially showed only moderately elevated thresholds but exaggerated subjective reactions at threshold levels. During treatment with topical application of capsaicin, a significant elevation in activation thresholds of the sensory- and pain receptors was found. At the same time, a positive subjective reduction of the pain was registrated. Of the treated patients, 62% reported at least some effect of capsaicin cream. This indicates, in spite of initial subjective discomfort, that capsaicin treatment may be useful for patients with PHN, in which no other treatment modality has proven effective.

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