LETTERS TO THE EDITOR

Topical Capsaicin Response as a Phenotypic Measure in Patients with Pain

Dear Editor:

Capsaicin, the active component of chili peppers, selectively activates TRPV1 transient receptor potential cation channels, expressed primarily by a subpopulation of afferent C-fibers [1]. Local topical or intradermal application of capsaicin causes burning pain, neurogenic inflammation, hyperalgesia, and a vascular flare response [2]. It yields rather reproducible pain responses in healthy volunteers [3] and is used as an experimental human pain model. More recently, Campbell et al. reported that an increased pain response to capsaicin application is associated with a better treatment response to topical clonidine in painful diabetic neuropathy, presumably linking the capsaicin response to small fiber function [4].

The pain response to capsaicin involves central processing of afferent input and can be modified by placebo manipulation [5], which is activated via descending pain control pathways [6]. Vasodilation, conversely, is mediated by local release of vasoactive mediators such as the calcitonin gene-related peptide (CGRP) and substance P, and does not require cortical processing [7,8]. Hence, for the purpose of functional small-fiber assessment in pain patients, objective measurement of local flare responses may provide a more reliable method. We performed an ad-hoc analysis of data from our recently completed study [9], which may elucidate the difference between assessing objective local flare responses and patient-reported pain following topical capsaicin application.

The study was approved by the Regional Research Ethics Committee of Central Denmark (1-10-72-31-12) as part of a research project involving patients with unilateral neuropathic pain in a foot due to peripheral nerve injury [8]. Written informed consent was obtained from each patient prior to participation.

All patients underwent quantitative sensory testing (QST) according to the German Research Network on Neuropathic Pain protocol [10]. At baseline, 1 mL of topical 10% capsaicin cream was applied to both (painful and non-painful) dorsal feet (circular 1 cm diameter application). The skin temperature was maintained at 34°C by a feedback lamp. The patients’ pain responses were measured on 0–100 numerical rating scale (NRS) before and every 5 minutes for 30 minutes after capsaicin application. In addition, the local vascular flare response was measured by laser Doppler imaging before and 30 minutes after the application [11].

On a separate day, the patients underwent an ultrasound-guided peripheral nerve block with 2% lidocaine in the affected extremity, resulting in a complete abolition of spontaneous and evoked foot pain [9]. Ninety minutes after the block, while patients still experienced complete pain relief, capsaicin application on both feet was repeated. Lidocaine plasma concentrations were measured at 7 time points up to 120 minutes after the block.

Six patients participated in this study. The mean age was 51 (range 18–67) years and 5 patients were male. The neuropathic pain was due to a traumatic (N = 3) or a surgical (N = 3) nerve injury to the peroneal, the tibial, and/or the sural nerves, with median spontaneous pain intensity of 6.5 (range 5–8) on the 0–10 NRS. The QST findings were normal in the non-injured feet, and abnormal in the painful feet, with details described elsewhere [9]. At baseline, the pain intensity at 30 minutes after capsaicin application on the nonpainful foot was 24.2 ± 27.6 (on 0–100 NRS), and the local flare response measured by laser Doppler was 249.8 ± 138.2 (flux units).

After peripheral nerve block has abolished the ongoing pain, capsaicin application on the contralateral (nonpainful) foot resulted in pain intensity of 42.5 ± 22.1, a 75.6% increase from baseline (P = 0.050; Student’s t test, normality passed by Shapiro–Wilk test, 0.918) (Figure 1). The area under the pain intensity vs time curve (AUC) over 0–30 minutes was 657.1 (vs 356.2 at baseline; Figure 2). The local capsaicin-evoked flare response measured by laser Doppler flux did not change significantly (232.1 ± 98.3 during block vs 249.8 ± 138.1 at baseline (P = 0.68), nor did the mean area of flare (6.32 ± 2.3 cm² vs 6.57 ± 4.5 cm² at baseline (P = 0.63). In the ipsilateral (painful) foot, none of the patients experienced any spontaneous or evoked pain response when capsaicin was applied after the nerve block. The local vascular flare response to capsaicin in the ipsilateral foot could not be directly compared to the baseline assessment because of increased skin blood flow and temperature secondary to sympathectomy induced by the nerve block. No temperature changes were observed in the contralateral (unaffected) foot, and plasma lidocaine concentrations 0–120 minutes after the block were low (in all patients less than 1 mcg/mL).

Our findings of increased pain response after relief of contralateral pain by a nerve block suggest that the ongoing pain may diminish, or mask, the pain response.
associated with topical capsaicin administration, while the local vascular flare response is not affected by ongoing pain. plausible reasons for this phenomenon may be a distraction due to ongoing pain, or descending pain modulation, activated by the ongoing pain “conditioning.” the order of capsaicin application was not randomized and we cannot exclude the possibility of order effect on pain response intensity; however, other studies have not shown increase in pain response after repeated capsaicin applications [12,13]. it has been shown in animal and human studies that ongoing painful stimuli reduce the level of nociception or pain associated with a different (second) noxious stimulus [14–16], a phenomenon known as diffuse noxious inhibitory controls or conditioned pain modulation. in a study by campbell et al. [4], the patients who had high pain response to capsaicin at baseline demonstrated diminished analgesic response to placebo; and as placebo analgesia may be related to activation of the descending pain pathways [6], this may suggest that pain intensity following capsaicin application in patients with ongoing pain is affected by the efficiency of their conditioned pain modulation response. it is important to note that the response to topical capsaicin is not straightforward and is affected by the underlying pain condition and small fiber morphology [11,17,18]. the results of this small study suggest that the pain response to capsaicin represents a complex phenomenon, which may be affected by ongoing pain and needs further investigation. objective assessment of the local vascular flare response may provide a more reliable outcome measure in this scenario as it does not involve central processing, but the optimal methodology is yet to be determined in larger studies.

SIMON HAROUTOUNIAN, PHD,* LONE NIKOLAJSEN, MD, DMSc,† NAPPA B. FINNERUP, MD, DMSc,† TROELS S. JENSEN, MD, DMSc†§
*Division of Clinical and Translational Research, Department of Anesthesiology, Washington University School of Medicine, St Louis, MO 63110; †Danish Pain Research Center, ‡Department of Anesthesiology and §Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

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**References**


Seizures and Transient Neurological Deficits During Epiduroscopy in a Patient with Failed Back Surgery Syndrome

Dear Editor:

Although epiduroscopy is a minimally invasive technique, reports pertaining to its clinical use and complications are incomplete [1]. We herein present a case study of a patient who experienced seizure and transient neurological deficits during epiduroscopy.

A 42-year-old male patient was admitted to an algology clinic with bilateral back and leg pain that was more pronounced in the right leg. According to his medical history, the patient underwent lumbar stabilisation operations in February 2009, but the pain returned following the operations and continued to increase (Figure 1). By the time we saw the patient, his visual analog scale (VAS) pain rating was 9/10. The patient’s straight leg-raising test performance was normal. There was no neurological deficit, but neuropathic symptoms, including constant burning and tingling, were present especially in the right leg. The patient, whose complaints did not abate despite the use of 300 mg/day pregabalin and 200 mg/day tramadol, did not benefit from physical therapy. Therefore, a fluoroscopy-guided caudal epidural steroid injection was administered. Epiduroscopy was undertaken when the patient’s complaints, which decreased for a month through this procedure, returned to a similar level of severity, with a VAS pain rating of 6/10.

The intervention site was cleaned with an iodine-based antiseptic solution in the prone position. Conscious sedation was achieved via 1–2 mg midazolam, 25–50 mg fentanyl, and 30 mg/kg propofol. The intervention site, skin,