

Persistent neuropathic pain treated with capsaicin patches: a novel promising approach

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Abstract

Neuropathic pain is associated with a functional abnormality of the nervous system due to a direct lesion or disease of the somatosensory system, leading to a continuous pattern of pointless and detrimental pain signal: the pain itself rather than the predisposing condition becomes the main pathological element.

In this framework, capsaicin has been used in several clinical settings as a topical medication to treat neuropathic pain. We report three cases of persistent neuropathic pain who underwent our protocol: three applications of the capsaicin 8% patch separated by one month.

In all the reported cases, the outcome has been a significant reduction of the symptoms, and the pain relief has maintained, staggered only by sporadic episodes of exacerbation.

The treatment is safe and effective in reducing the intensity of the pain, being a valid therapy for the treatment of the chronic neuropathic pain, administered in association with other drugs.

Keywords: Capsaicin, Neuropathic pain, Post herpetic neuralgia, Triple neurotomy, Causalgia.

Background

Neuropathic pain is associated with a functional abnormality of the nervous system, caused by a direct lesion or disease of the somatosensory system encompassing a large variety of etiologies [1]. The consequent changes in the nervous system consist of a continuous pattern of pointless and detrimental pain signal: the pain itself rather than the predisposing condition becomes the main pathological element. Neuropathic pain severity, however, is not correlated with the amount of nerve damage, and symptoms can persist long after the resolution of an antecedent injury.

Clinical features of neuropathic pain include the presence of an abnormal, unpleasant sensation, defined as dysesthesia, which frequently has a burning or electrical quality with an occasional paroxysmal, brief, shooting or stabbing quality. Moreover, neuropathic pain is commonly associated with phenomena of allodynia, which is the perception of pain following a not painful stimulus, hyperalgesia, an enhanced response to a mildly noxious stimulus, and causalgia, consisting of a chronic burning persistent pain without an obvious noxious stimulus [2].

Even though there are few therapeutic options for the aforementioned disease, the recommendations consider drugs which modulate the pattern of the nerve discharge.

Drugs proposed as the first line include tricyclic antidepressants (particularly amitriptyline), serotonin-norepinephrine reuptake inhibitors (particularly duloxetine), pregabalin and gabapentin. Second line treatments consist of lidocaine plasters and capsaicin high concentration patches for peripheral neuropathic pain only, and tramadol. Third line treatments involve strong opioids and botulinum toxin A (for peripheral neuropathic pain) [1].

Focusing on capsaicin, it has been used in several clinical settings as a topical medication to treat pain derived from different conditions. The USA regulatory authorities have approved capsaicin as an 8% dermal patch for treating local pain. These patches contain 640 mcg/cm² of synthetic capsaicin with a total dose of 179 mg in one patch [3].

Capsaicin(trans-8-methyl-N-vanillyl-6-nonenamide-C18H27NO3) is a naturally occurring substance derived from

the plants of the genus *Capsicum*, family Solanaceae and it is a vanilloid as it contains a vanillyl group in its formula. It selectively stimulates nociceptive neurons and has been widely used to study pain-related events. It has a nonpolar phenolic structure which allows a good absorption when administered topically or orally.

It has been demonstrated that capsaicin, like some physical activators and protons, activates TRPV1 (the transient receptor potential vanilloid subtype 1) [3], having a very high affinity, sensitivity, and selectivity for this channel thanks to specific amino acid residues involved in the binding [2]. TRPV1 activation leads to a rapid cationic ionic influx, including Na⁺ and Ca²⁺. Subsequently, its activation also modulates second messenger balance and organelles physiology, mainly mitochondria [4].

TRPV1 is an ion channel acting as a polymodal cellular sensor, which responds to several distinct agents, such as extracellular acidification and high temperatures. In fact, TRPV1 has been linked to thermic sensation, autonomic thermoregulation, nociception, food intake regulation and multiple functions in the gastrointestinal tract, but above all, concerning the CNS [3], this ion channel is mainly expressed in neuronal cells, as trigeminal nerves, and dorsal region ganglia [4].

Considering the structures of the nervous system, capsaicin has a selective action on C-polymodal nociceptors, also mediated by reactive oxygen species (ROS), which also are a source of post-translational modification due to their action on redox-sensitive protein residues such as cysteine and serine, suggesting a role of ROS in the maintenance of persistent pain. Nevertheless, the effects of capsaicin on nociception are not limited to its ability to produce pain. In fact, high or repeated doses of capsaicin induce an initial pain sensation, followed by analgesia. This loss of sensitivity to painful stimuli has been noticed in response to not only thermal, but also mechanical and chemical noxious stimuli. After exposure to a high or repeated dose of capsaicin, the TRPV1 receptors begin a refractory state commonly termed as desensitization which leads to inhibition of receptor function [4].

It has been demonstrated that capsaicin has other effects on neurons which are TRPV-1 independent: firstly, Capsaicin is a lipophilic alkaloid. Thus, its interaction with biomembranes may alter the plasma membrane fluidity by positioning between the lipid-water interfaces. Secondly, the participation of capsaicin in the respiratory chain occurs because it binds to complex-I and complex-III in the mitochondrial respiratory chain, blocking the electron transport. In consequence, capsaicin exposition evokes mitochondrial membrane potential disruption and increase in the mitochondrial membrane permeability. A reduction of cell viability after treatment with capsaicin is due to both reactive oxygen species generation and apoptotic-like cell death, whose cytotoxic effects are mediated by apoptosis through cytochrome c release, activation of caspases, and poly-ADP-ribose polymerase (PARP) cleavage. Finally, some studies indicated capsaicin participation in neurotransmission in a TRPV1-independent manner. It seems to be

able to modulate the synaptic transmission acting through pre- and postsynaptic mechanisms [5].

Case 1: A Patient with Post Herpetic Neuralgia: Presentation

We report a case of a 41 years-old male patient affected by persistent pain lasting for 1 year, due to post herpetic neuralgia involving the area covered by the supraorbital nerve, which derives from the frontal nerve, a branch of the ophthalmic nerve (Figure 1a).



Figure 1: A) The injured area has been encompassed with a pen.

Despite the different treatments he had undergone: gabapentinoids, amitriptyline, opioid analgesics, patches of lidocaine 5%, supraorbital nerve block, and electroacupuncture, the patient had only a partial and temporary relief, with associated incoercible itching.

Investigations and Differential Diagnosis

Postherpetic neuralgia (PHN) is a neuropathic pain syndrome caused by herpes zoster (HZ), a reactivation of the varicella zoster virus (VZV). It consists of neuropathic pain persisting for 6 months following the onset of HZ. Pathophysiological studies suggest that PHN describes a number of distinct patterns of neurological dysfunction including modulation of peripheral and central pain processing.

Because of the different mechanisms of injury involved, PHN tends to fall into a number of phenotypes, any or all of which may copresent:

- Constant pain without a stimulus, often described as burning, itching, or throbbing
- Intermittent pain without stimulus, often described as stabbing, shooting, or like electric shocks
- Evoked pain-allodynia and/or hyperalgesia.

Reactivation of the VZ virus in the sensory neuron causes an inflammatory response which damages both CNS (central nervous system) and PNS (peripheric nervous system). Firstly, in PNS, extensive neurodegenerative changes in the axons of both small and large diameter sensory nerves occur, followed by axonal demyelination and neuronal cell death leading to deafferentation and fibrosis [6]. This causes generalized necrosis and cell death in the skin (and sometimes in the CNS) and within the nerve, root, and ganglion. Being damaged, the peripheral nerves lose the ability to inhibit nociception pain signaling, lowering the threshold

for nociceptive pain activation, and producing spontaneous ectopic discharges. The result generates disproportionate pain with non-painful stimuli, a phenomenon known as peripheral sensitization. At the cellular level, PHN upregulates the receptors typically associated with pain, such as TRPV1, also increasing the proportion of voltage-gated sodium channels and potassium voltage-gated channels. There is also evidence of loss of γ -aminobutyric acid inhibitory interneurons at the dorsal horn in addition to loss of descending inhibition [7].

Beyond the complex neuropathophysiology, PHN culminates in a significant physical, social, and emotional burden, as pain often interferes with sleep and is associated with cognitive impairment. Other associated symptoms are decreased appetite, weight loss, decreased physical activity, depression, and anxiety. Although sensory neurons are primarily involved, occasionally motor function can be affected by extensive spread of the damaging inflammatory processes [6].

Treatment

When the patient came to our Center, after the careful examination, he underwent the protocol of the treatment of neuropathic pain with capsaicin, which consists of three applications of the capsaicin 8% patch separated by a span of time of one month (Figure 1b and 1c).



Figure 1: B) Capsaicin 8% patch QUTENZA® has been put on the affected area; C) the skin after the application of the patch showing the effect of capsaicin.

Outcome and Follow-Up

The outcome has resulted to a significant reduction of the symptoms, persisting also in the 1-month follow-up (Figure 2-9): the pain relief has maintained, staggered only by sporadic episodes of itching.

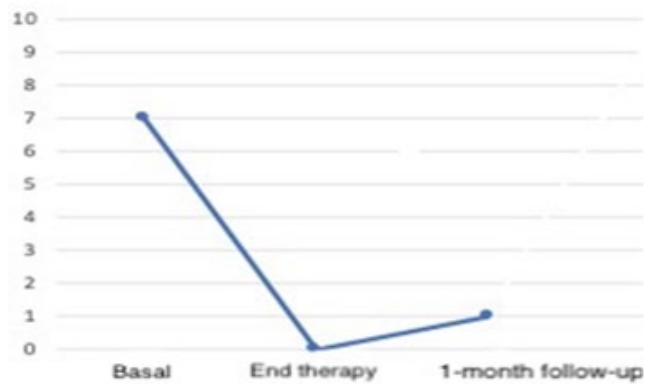


Figure 2: Visual Analogue Scale (VAS) of pain before the treatment, at the end and at the 1-month follow-up control.

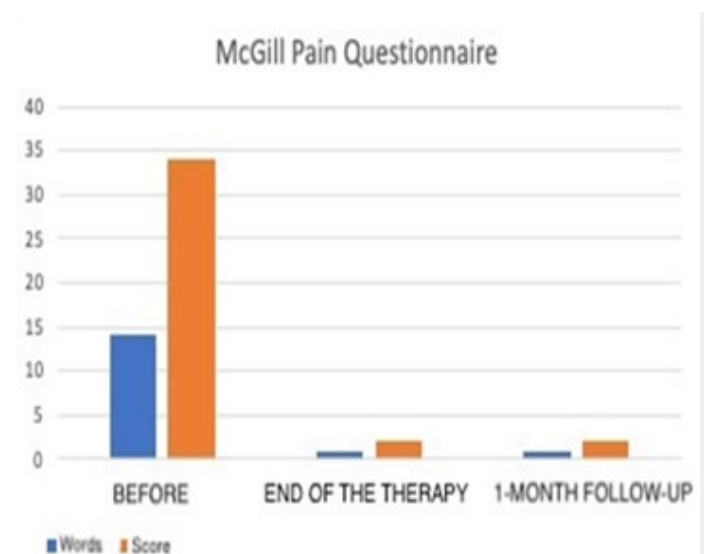


Figure 3: McGill Pain Questionnaire (MPQ) assessing both quality and intensity of subjective pain before and after the treatment, and at the 1-month follow-up control.



Figure 4: A) Delimitation of the area of allodynia; B) Application of topic local anesthetic (EMLA) for 1 h; C) Application of capsaicin patch on the delimited area.

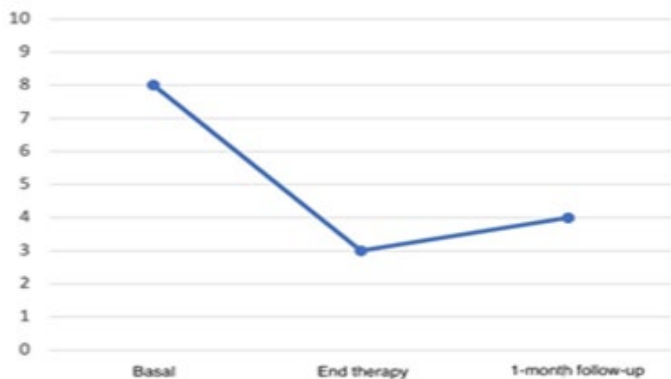


Figure 5: Visual Analogue Scale (VAS) of pain before the treatment, at the end and at a follow-up control.

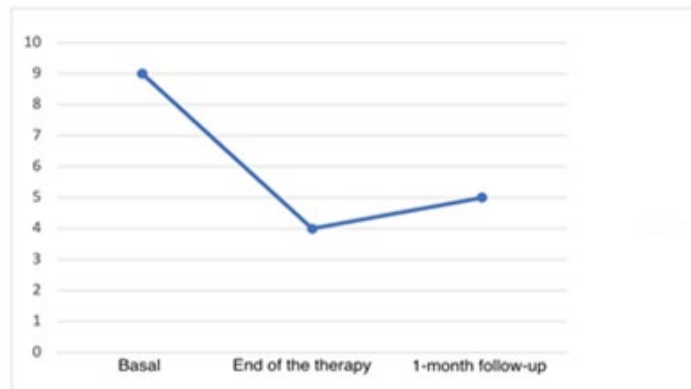


Figure 8: Visual Analogue Scale (VAS) of pain before the treatment, at the end and at a follow-up control.

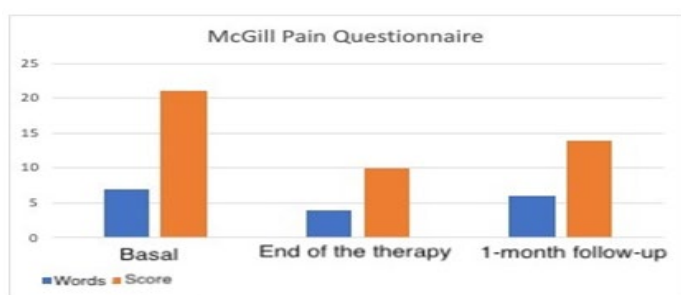


Figure 6: McGill Pain Questionnaire (MPQ) assessing both quality and intensity of subjective pain before and after the treatment, and at a follow-up control.

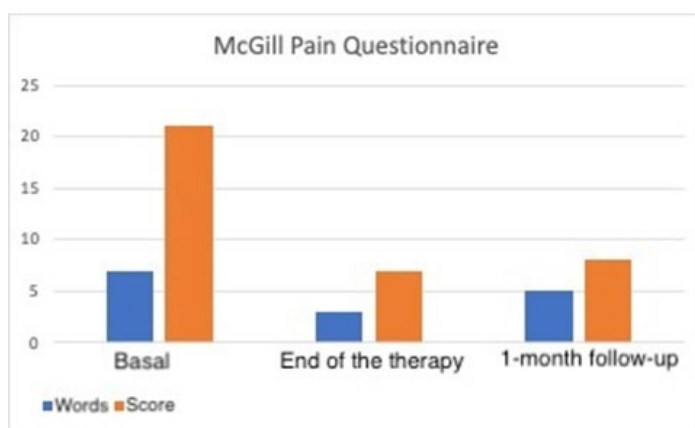


Figure 9: McGill Pain Questionnaire (MPQ) assessing both quality and intensity of subjective pain before and after the treatment, and at a follow-up control.



Figure 7: A) delimitation of the area of allodynia; B) application of topical local anesthetic (EMLA) for 1 h; C) application of capsaicin patch on the delimited area.

Case 2: A Case of Pain Consequent to Deafferentation: Presentation

A 32 years-old male patient has had painful consequences post triple neurotomy for 48 months. Throughout this span of time, he had undergone the following therapies: gabapentinoids drugs, amitriptyline, opioid analgesics, patches of lidocaine, local infiltrations, acupuncture, PENS. Nevertheless, the pain is reported to be in the right inguinal area, episodic with allodynia and hyperalgesia.

Investigations and Differential Diagnosis

Chronic post-inguinal herniorrhaphy allodynia consists of a chronic neuropathic pain after retroperitoneal inguinal hernia repair. This chronic neuralgia is easily distinguished from normal postoperative pain: the latter occurs immediately after surgery and is easily treated with analgesics. Chronic neuralgia, indeed, could well be unresponsive to medical therapy, often becoming a debilitating pain that includes paresthesia, hypoesthesia, and dysesthesia. Many patients with this complication also have other problems, such as mood swings, depression, or long-term drug dependency,

and often are unable to return to work. Resection of the ilioinguinal, iliohypogastric, and genital nerves is an established procedure for permanent elimination of postherniorrhaphy neuralgia [10]. Even though surgery is often offered as a final treatment option, Henrique postoperative neuropathic pain persists after 6-12 months, it is important to consider that neuralgia might persist after surgery, due to neuroplasticity, afferent hypersensitivity or centralization of pain [8].

Treatment

The above-mentioned protocol of treatment of neuropathic pain with Capsaicin, consisting of three applications of the capsaicin 8% patch on the affected area, separated each other by a span of time of one month has been employed.

Outcome and Follow-Up

The clinical outcome at the end of the therapy consists essentially of a reduction of 50% of the initial pain. However, during the follow-up of one month, some episodes of exacerbation of the pain occurred, but their entity was significantly lower.

Case 3: A Case of Causalgia: Presentation

A 20-years old female patient came to our out-patients presenting persistent pain in the left ankle in CPRS-I consequent to a distorsive trauma occurred in 2016 after which she underwent a treatment with neridronate following the protocol.

Due to the persistence of the pain and the occurrence of synostosis calcaneonavicular left, on the 13th January 2018 she underwent a surgical repair consisting of asportation of synostosis and application of endorthesis senotarsic. After the surgery, the pain has never relieved, and the typical CPRS-I vasomotor symptoms of the skin persisted. In consequence, she underwent several diagnostic procedures including RM and triphasic scintigraphy, which have confirmed the diagnosis of CRPS-I, causing the stabilized outcomes and signs of bone remodeling. Hence, she underwent the following treatments: pharmacologic analgesic and anti-inflammatory therapy, which have come out to be not effective enough.

Moreover, lumbar sympathetic nerve blocks cycles, a cycle of electro-acupuncture, infusion I.V. Ketamine, and treatment with pulsed RF of sural nerve and superficial peroneal nerve, have been performed, but they have resulted to be poorly effective too. In July 2020 the woman underwent the implantation of a perinervous neurostimulator on sural nerve, with acceptable control of the pain, but without relief from the vasomotor manifestation and the persistence of hyperalgesia cutaneous. Currently, the pin is located in the submalleolar surface of the left ankle, with hyperalgesia in correspondence to the scar.

Investigations and Differential Diagnosis

CRPS can be described as a painful inflammatory condition which occurs in most cases after a traumatic lesion, such as a sprain or fracture. The main physio pathological elements involved in

genesis of CPRS-I are essentially: autonomic nervous system activity, neurogenic inflammation and micro vascular impairment. However, in this framework, the sympathetic nervous system plays a pivotal role in the pathophysiology: the expression of $\alpha 1$ -adrenoceptor mRNA is up regulated in DRG neurons after peripheral nerve injury or inflammation typical of what is seen in CRPS type I; and an increase in $\alpha 1$ -adrenoceptors is observed in hyperalgesic skin of patients affected [9].

Treatment

She underwent the protocol of treatment of neuropathic pain with Capsaicin, which includes three applications of the Capsaicin 8% patch on the affected area, separated each other by a span of time of one month.

Outcome and Follow-Up

After an initial stage of worsening of symptoms, we have detected a reduction of the intensity of the pain and of the extension of the affected area. Nevertheless, the cutaneous vasomotor manifestations persisted.

Discussion

In this work, three cases of persistent neuropathic pain resistant to pharmacological and infiltrative therapy are described, on which the treatment applied has been demonstrated effective in reducing the intensity of the pain and the extension of the painful area.

This is a notable achievement, because the unresponsive pain has a considerable impact on the quality of life: the pain relief allows a significant improvement of quality of life and is in fact the fundamental parameter to consider when it comes to the chronic disabling pain, besides of the intensity of the pain itself. In this context, the use of capsaicin patch 8% is considered a useful treatment in chronic neuropathic pain.

In the three cases reported, we have employed a different method of administration from the medical indication of the drug, deriving from data reported in literature: currently, in repeated application of capsaicin patch, Guidelines recommend a time interval of 8-12 weeks between the applications [11]. This therapeutic strategy is demonstrated to be effective in pain relief also in cases of resistant persistent pain.

Nevertheless, our promising results obtained employing a time span of 4 weeks between the applications of the patch, could well be related to the fact that reinnervation of the epidermis by ENFs began during the third and fourth weeks after the capsaicin injection and was characterized by the return of an intact subepidermal neural plexus and the reappearance of sparse nerve fibers in the epidermis [12].

Moreover, the treatment is safe, as it did not produce any adverse events either in regions where a cautious application is strongly recommended, like the eyebrow and inguinal area, or for the closer span of time than the three months recommended between the

applications.

The pain relief persisted in the long-term follow-up reducing the impairment of the quality of life.

Take Home Messages

- ✓ The treatment is effective in reducing the intensity of the pain, and it consists of a valid therapy for the treatment of the chronic neuropathic pain administered in association with other drugs.
- ✓ The applications of the capsaicin patch 8% separated by a shorter time span (4 weeks) should be considered in cases of resistant pain.
- ✓ The treatment is safe and free from any side effects.

Declarations

Written informed consent was obtained from all patients. All methods were carried out in accordance with relevant guidelines and regulations of ethical principles for medical research involving human, stated in the Declaration of Helsinki

Availability of Data and Materials

All data generated or analysed during this study are included in this published article

Consent for Publication

Not applicable.

Availability of Supporting Data

The data that support the findings of this study are openly available.

Competing Interests: I declare that the authors have no competing interests, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

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Authors' Contributions

G.G. conceived the original idea. V.G. developed the theory and performed the computations.

A.B. and F.C. verified the analytical methods. G.G., A.B. and G.F. carried out the experiment.

G.G. and F.C. supervised the findings of this work.

All authors discussed the results and contributed to the final manuscript.

Patient's Perspective

All patients have been adherent to the treatment and have expressed at the end a moderately high level of satisfaction.

Patient 1: "I am satisfied. There is no more either itching or painful areas".

Patient 2: "the pain has significantly reduced, but it is still present.

My quality of life is significantly improved, so I am satisfied enough".

Patient 3: "The shocking component of the pain has disappeared, but the pain, even though with moderate intensity, still persists".

(Translated from Italian)

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