Observational Study

Use of High-Concentration Capsaicin Patch for the Treatment of Pelvic Pain: Observational Study of 60 Inpatients

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Background: Chronic pelvic, perineal and gluteal neuralgia is often experienced in a similar way to neuropathic pain, in the territories of four nerves: ilio-inguinal, pudendal, inferior cluneal and posterior gluteal nerves. These pains are often refractory to medical treatment based on the use of systemic molecules with disabling adverse effects and surgical procedure may be necessary.

Objective: The objective of this study was to evaluate the efficacy and safety of treatment with a high-concentration capsaicin patch in these indications.

Study Design: This study was prospective, nonrandomized, and observational.

Setting: Federative Center of Pelvi-Perineology in the University Hospital of Nantes, France.

Methods: Sixty patients with pelvic neuralgia were treated with high-concentration capsaicin patch. The primary endpoint was Patient Global Impression of Change (PGIC) and secondary endpoints included pain intensity on a Numerical Rating Scale (NRS), maximum sitting duration at the end of the day, Medication Consumption Score (MQS), and patient global improvement (from -100% to + 100%).

Results: Twenty four percent of the 60 patients included in the study declared that they felt "very much improved" or "much improved" (PGIC = 1 or 2) and these patients reported an average 58% improvement and a 3.4-point reduction on the NRS. Among the "good responder" patients, patients with coccygodynia appear to obtain the best results, as 37% of these patients declared that they were much improved with an average 63% improvement No serious adverse effects were observed and treatment was well tolerated.

Limitation: This study is limited by its relatively small sample size and non-randomized study.

Conclusion: These results suggest the value of high-concentration capsaicin 8% patch in the treatment strategy for patients with chronic pelvic, perineal and gluteal neuralgia. This treatment would be particularly indicated in the management of coccygodynia.

Key words: Pelvic pain, neuropathic pain, pudendal nerve, ilio-inguinal nerve, inferior cluneal nerve, posterior gluteal nerve, capsaicin, capsaicin patch, coccygodynia

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Chronic pelvic, perineal, and gluteal neuralgia is often experienced in a similar way to neuropathic pain, mainly in the form of burning pain or, more rarely, numbness, prickling, tingling, or electrical shocks, associated with allodynia (1).

This pain corresponds to the territories of 4 sensory nerves: 3 sacral nerves and one thoracolumbar nerve (Fig. 1):

- The territory of the pudendal nerve, from the anus to the glans or clitoris
- The territory of the posterior cutaneous nerve of the thigh and its inferior cluneal branch, from the buttock and infragluteal fold to the perianal region
- The territory of the posterior gluteal nerve innervating the sacrococcygeal region
- The territory of the ilioinguinal and iliohypogastric nerves including the groin, suprapubic region, and anterior third of the perineum (of thoracolumbar origin).

These territories partially overlap.

The etiologies of chronic perineal neuralgia can be:

- neoplastic and malformative
- post-traumatic (post-surgery, fractures of the coccyx or sacrum)
- nerve entrapment syndromes (pudendal, cluneal neuralgia)
- obstetric
- idiopathic, such as certain forms of coccygodynia and vestibulodynia.

Qutenza® (GP Grenzach Produktions GmbH, Emil Barell Strasse 7D-79639 Grenzach-Wyhlen, Germany), high-concentration capsaicin 8% cutaneous patch obtained European marketing Authorization in 2009 for the treatment of peripheral neuropathic pain in nondiabetic adults and has been approved in the USA by the FDA (Food and Drug Administration) for post-herpetic pain.

The primary objective of this study was to evaluate the efficacy of this treatment in the management of pelvic, perineal, and gluteal neuropathic pain. The secondary objective was to evaluate the safety of this treatment.

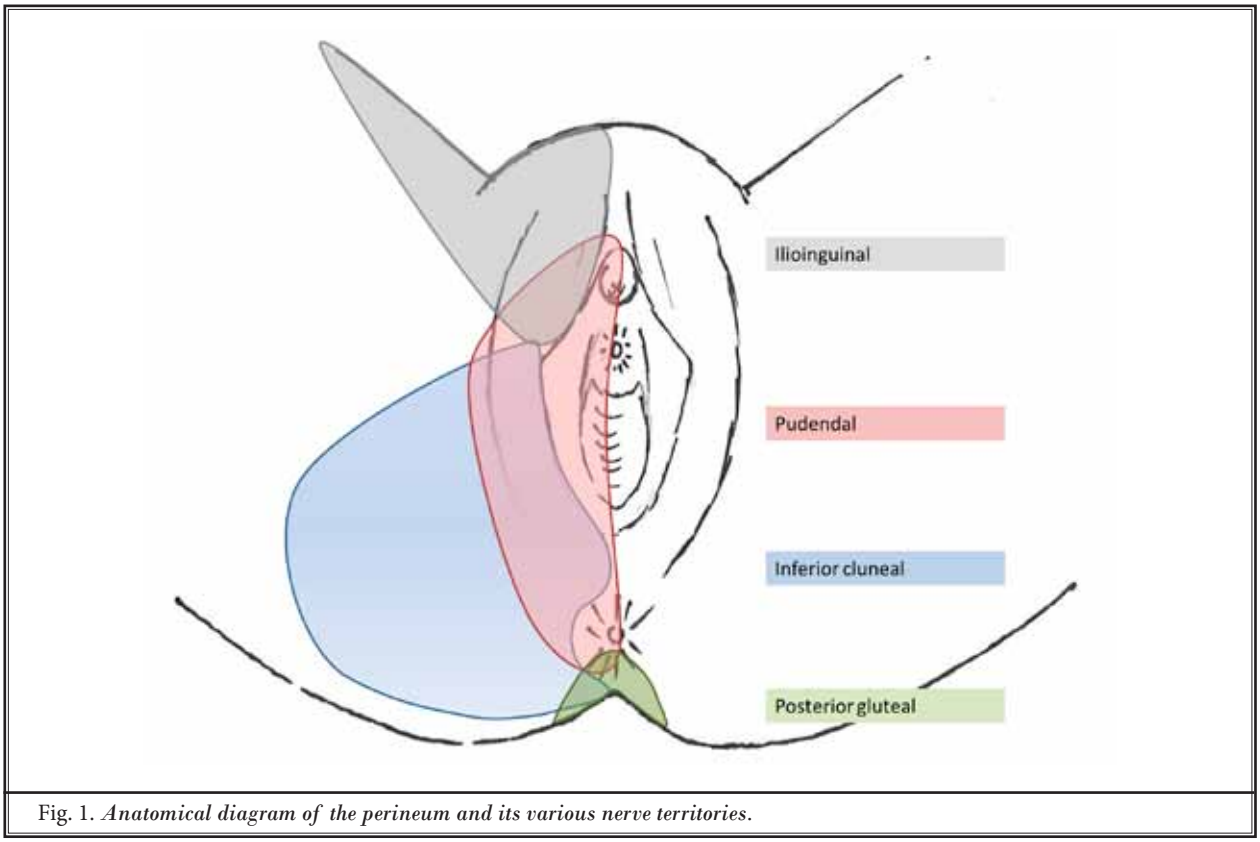

Fig. 1. *Anatomical diagram of the perineum and its various nerve territories.*

Methods

Patients

This observational cohort study was conducted on patients consulting the Nantes University Hospital Pelviperineology unit for chronic (> 3 months) neuropathic pain (burning, prickling, tingling, allodynia), in one of the 4 pelvic, perineal, and gluteal nerve territories (ilioinguinal, pudendal, inferior cluneal, and posterior gluteal) treated with capsaicin 8% cutaneous patch.

Efficacy Endpoints

The primary endpoint was the 7-point PGIC (Patient Global Impression of Change, see Appendix 1) at 2 months.

Secondary endpoints were the variation, after 2 months, of:

- pain intensity measured by a pain numerical rating scale (NRS from 0 to 10)
- maximum sitting duration at the end of the day (after 6:00 p.m.)
- medication consumption defined by the MQS (Medication Quantification Scale)
- patient global improvement expressed as a percentage (from -100% to +100%).

Safety Endpoints

Safety was evaluated during a half-day hospitalization by the variation of pain intensity (NRS) between the patient's admission and discharge and a procedure discomfort score (from 0 to 10) at the time of the patient's discharge from hospital.

Statistical Analysis

Significant differences were tested by Wilcoxon rank tests on paired data.

Procedure for Using the Capsaicin 8% Patch in the Pelviperineal Region

The capsaicin 8% patch is contingent upon a health care practitioner during a half-day hospitalization. Capsaicin is volatile and highly irritating. Manipulating the capsaicin 8% patch requires professional training and is reserved for nurses in a pain management center (2).

The use of a capsaicin 8% patch requires no washout period. It can be used alone or in combination with other treatments for neuropathic pain.

The 14 cm x 20 cm (280 cm2) patch must cover the zone to be treated and a maximum of 4 patches can be applied simultaneously for a duration of 60 minutes. Capsaicin must not be applied adjacent to mucous membranes due to its highly irritant property. Mucous membranes were therefore protected by a layer of petroleum jelly covered by a dry compress. In order to limit the intense burning sensations induced by capsaicin, cold packs were also applied to the treated zone before (10 minutes), during, and after (10 minutes) application of the patch.

According to the duration of action from a single application observed in the princep study, we proposed to treat patients every 3 months (3).

Results

This study was conducted on 60 patients. The patient distribution according to the site of pain is shown in Fig. 2. Twenty-five patients (40%) had a history of unsuccessful pudendal and/or cluneal nerve release surgery.

Efficacy

The results concerning the primary endpoint, PGIC, are presented in Fig. 3. Fourteen (24%) of the 60 patients declared that they were "very much improved" or "much improved" (PGIC = 1 or 2) compared to before treatment.

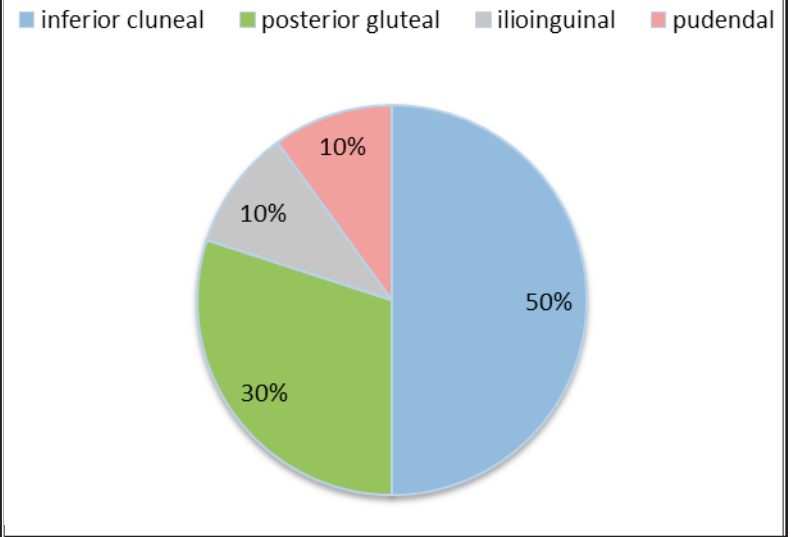

Fig. 2. *Distribution of nerve territories involved, n = 60 patients.*

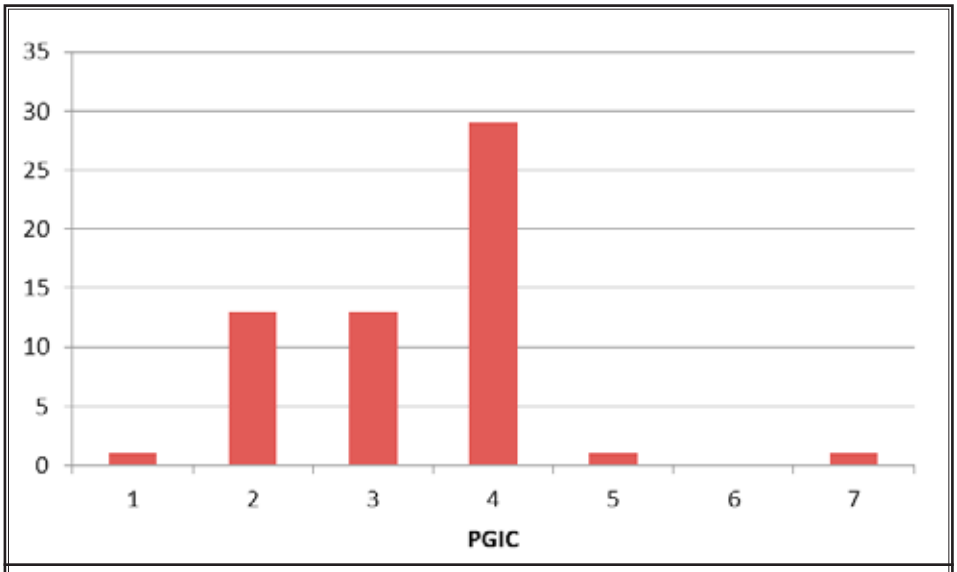

Fig. 3. *Patient evaluation of the efficacy of treatment, n = 60.*

PGIC = Patient Global Impression of Change, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse

The mean percentage improvement in this population was 58% (29.9) compared to 24% (± 31.1) in the overall cohort.

The variation of pain intensity at 2 months in the overall cohort was -1.08 points (± 2.6) (*P* = 0.006), the variation of maximum sitting duration at the end of the day (after 6:00 p.m.) was + 0.39 hours (*P* = 0.001), i.e. + 24 (± 26.1) minutes and MQS decreased by 0.53 (*P* = 0.17) with a range of 0 to 42.

Among the patients with a good response to treatment (PGIC = 1 or 2), the mean reduction of pain intensity on the NRS was 3.4 points (± 1.8) (*P* = 0.001) and their sitting duration after 6:00 p.m. was increased by a mean of 54 minutes (± 79.8) (*P* = 0.02). The MQS decreased by 0.3 points (± 3.7) (*P* = 0.7).

Safety

The mean variation of pain intensity on the day of the procedure was + 0.15 points on a 10-point scale (± 3.6) (*P* = 0.0.57). The mean procedure discomfort score (missing data for 10 cases) was 3.9/10 (standard deviation: 2.8). Eight patients (16%) reported a discomfort score greater than 7/10. Patients primarily reported burning sensations in the treated area and for one patient burning sensation in both lower limbs. These side effects have persisted on average 12 hours and 10 days maximum.

Discussion

Capsaicin is a highly selective ligand of TRPV1 vanilloid receptors, largely involved in nociceptive transmission. Ion channels present on Aδ and C fibers modulate the sensitivity of afferent neurons by regulating the influx of ions across the cell membrane (4). Prolonged exposure of these receptors to a high concentration of capsaicin induces pain desensitization in the treated zone. The pharmacodynamic mechanism has not yet been fully elucidated. Treatment with high-concentration capsaicin patch has been shown to decrease the density of cutaneous nociceptive fibers (3) and pain desensitization following application of the patch can be attributed to decreased expression of TRPV1 receptors.

Stimulation of cutaneous TRPV1 nociceptors induces a feeling of heat and erythema due to the release of vasoactive neuropeptides. It was initially recommended to apply a local anesthetic to the zone to be treated before applying a high-concentration capsaicin patch, but this procedure was long and ineffective and it was finally recommended to simply apply ice before (10 to 20 minutes), during and after application of the patch (5-7). This "natural premedication" has been shown to be very effective to limit burning and is much easier to apply. As capsaicin 8% patch is a topical treatment, the most common adverse reaction is a burning sensation on the skin.

The therapeutic efficacy and safety of capsaicin 8% patch in the treatment of neuropathic pain in adults have been evaluated in 4 pivotal multicenter randomized double-blind trials and one long-term open-label safety study in support of the marketing authorization application (8-12).

These trials demonstrated a mean 30% reduction in pain intensity and at least 30% improvement for 40% of patients. These trials were conducted in various indications and sites and were often based on different endpoints (13).

Our results concerning efficacy are slightly poorer than those reported in the literature. However, several explanations for this difference can be proposed:

1. The primary endpoint in our study (PGIC = 1 or 2) was more stringent, i.e. less sensitive but more specific, than those used in the literature. According to the endpoints commonly used in the literature (> 30% improvement), 35% of the patients in the present study improved (36% had a second treatment after 3 months and 12% a third re-treatment). Furthermore, a very significant improvement (58%) was obtained in the group of responders.
2. The population of patients included in our study was refractory to medical management comprising drugs (antiepileptics and/or antidepressants, step II analgesics), infiltrations, and physiotherapy, including transcutaneous electrical nerve stimulation. Moreover, 40% of patients were not relieved or insufficiently relieved by surgical management (pudendal and/or inferior cluneal nerve release or transposition).
3. Most patients had a particularly long history of pain (40% of patients had received medical treatment followed by surgery). Our results must therefore be interpreted by taking into account the psychological (anxiety-depression), somatic (pain sensitization), and social (unemployment, isolation) repercussions of chronic pain.

Application of the high-concentration capsaicin patch to the pelvic, perineal, and gluteal region was well tolerated despite the proximity of mucous membranes. Variation of pain intensity immediately following application was not clinically or statistically significant: + 0.15 point (± 3.6) (P = 0.057). No serious adverse reaction was observed (drug eruption, hyperalgesia, prolonged hospitalization, more intensive analgesic treatment, etc.). Patients attributed a mean procedure discomfort score of 3.9/10 (± 2.8). The proximity of mucous membranes therefore does not represent a contraindication, provided certain precautions are observed (petroleum jelly and dry compresses). However, 8 patients reported a procedure discomfort score greater than 7/10. These patients presented a mean baseline pain intensity of 7.14 points on the NRS versus 5.8 points for the overall cohort. Excessively high baseline pain intensity may therefore accentuate the perceived discomfort of the treatment.

Placement of the high-concentration capsaicin patch in the management of neuropathic pain:

Neuropathic pain is often refractory to medical treatment (14-16) based on the use of systemic molecules: tricyclic antidepressants, sertonin-norepinephrine reuptake inhibitors, and antiepileptics, which may be responsible for disabling adverse effects, sometimes preventing administration of the recommended effective dose (17,18). In some cases, a surgical procedure designed to release the nerve may be necessary, as in the case of typical pudendal neuralgia due to pudendal nerve entrapment and some forms of postoperative neuropathic pain when the identified cause is related to prosthetic material or fibrotic scar tissue. Although the results of surgery are satisfactory, 30% of patients do not improved and continue to experience pain one year after surgery (19).

Among the "good responder" patients, patients with coccygodynia appear to obtain the best results, as 37% of these patients declared that they were much improved (PGIC < 2) with an average 63% improvement (Fig. 4). Four patients (6%) with coccygodynia received only one application with a total and lasting relief of pain.

We examined the potential explanations for this tendency. The sacrococcygeal zone is a superficial zone with no muscle interface between the skin and bones and ligaments. The network of nerve endings targeted by topical capsaicin treatment would therefore be more readily accessible.

Medical treatment of coccygodynia remains insufficient in many cases. Systemic analgesics and co-analgesics present a poor benefit/risk balance in these cases of very localized pain and sacrococcygeal joint infiltrations are only indicated in the case of joint instability, intervertebral disc disease, or associ-

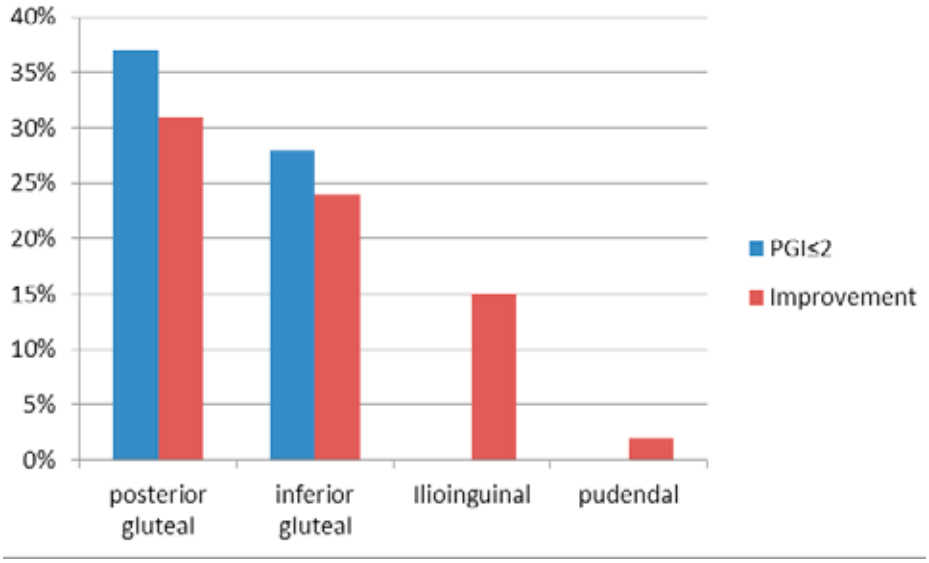

Fig. 4. *PGIC and percentage improvement in the various nerve territories.*

ated soft tissue lesions, i.e., in less than 50% of cases. Surgery (coccygectomy) must only be considered in the presence of disabling instability after failure of medical management due to its invasive nature and the risk of long-term deafferentation pain (20).

Due to the small number of alternative treatment options for patients with neuropathic coccygodynia, the history of pain in this group of patients was shorter than that observed in the other groups, which could possibly explain the poorer response in the pudendal, ilioinguinal, and inferior cluneal groups, in which many treatments including surgery (40% of the cohort) had already been tried without success.

Conclusion

The capsaicin 8% patch significantly improved pain in 24% of the patients in this cohort (mean improvement 58%) with particularly disabling chronic pain, refractory to appropriate management. These results are similar to those found in the literature for other treated areas. This justifies the place of high-concentration capsaicin patch in the treatment strategy for patients with chronic pelvic, perineal, and gluteal pain. In view of its good safety and the negligible risk of serious adverse reactions (none observed in this study), the capsaicin 8% patch could be proposed as a first-line treatment, especially in patients with coccygodynia.

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