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Capsaicin 8% patch: treat the pain and regenerate the nerves

Aims: To assess the mechanisms of pain relief following application(s) of the capsaicin 8% patch in patients with painful diabetic peripheral neuropathy (PDPN) and study the effect of this treatment on nerve regeneration in PDPN and non-painful diabetic peripheral neuropathy (NPDPN)

Methods: 50 patients with PDPN (average pain intensity ≥4/10 for spontaneous pain) were randomized to receive 30-min capsaicin 8% patch (Qutenza) application to both feet up to the distal calf, together with their standard of care treatment for neuropathic pain (PDPN Q+SOC group; n=32), or standard of care alone (PDPN SOC group; n=18). 25 NPDPN patients were enrolled and received 30-min Capsaicin 8% patch application. The patients performed pain diary, questionnaires, quantitative sensory testing (QST), and skin biopsies at baseline and after three months. Skin biopsies were performed within the area of capsaicin 8% patch treatment in order to study structural nerve marker (PGP 9.5), growth associated protein (GAP-43) (marker of regenerating nerve fibers) and von Willebrand factor.

Results: About the symptoms, there was a significant reduction in the average daily numerical pain rating score 3 months after capsaicin 8% patch application for the PDPN Q+SOC group (mean difference −1.87, p=0.0001) and in the SF-McGill Questionnaire (SF-MPQ-2) (in the overall pain score −31.1, p=0.002). No significant change was found for the SOC group for both the investigations. Only for the NPDPN Q+SOC group, an improvement of sensation at 3 months after the treatment (p=0.002) was recorded using Patient's Global Impression of Change.About the QST, PDPN Q+SOC showed a statistically significant improvement of warm perception threshold that positively correlated with the improvement in the overall pain score of SF-MPQ (p = 0.04). No change was observed in thresholds in the PDPN SOC group while NPDPN Q+SOC group showed a not statistically significant trend toward an improvement of the warm threshold. Skin biopsies showed an increase of intra-epidermal nerve fibers (IENF) with PGP9.5 at 3 months in PDPN Q+SOC (p=0.0002) and NPDPN Q+SOC (p=0.002) groups, but not in the PDPN SOC group. Increased sub-epidermal nerve fibers were observed with GAP43 in PDPN Q+SOC group (p=0.003) and NPDPN Q+SOC group (p=0.0005). Pain relief in the PDPN Q+SOC group correlated with the increased PGP9.5 IENF (p=0.0008) and GAP43 (p=0.004), whereas those who reported no pain reduction did not show any increase of PGP9.5 IENF, PGP9.5 SENFor GAP43.

Conclusions: Capsaicin 8% patch can provide pain relief via nerve regeneration and restoration of function in DPN.

Comments. Loss of sensory nerve fibers is one of the major contributors to the development of non-healing of foot ulcers, leading to amputations (Bus SA et al *Diabetes Metab Res Rev. 2020;36 Suppl. 1:e3269*). This complex and well-designed study suggests that the capsaicin 8% patch could potentially stimulate nerve regeneration in patients with diabetic peripheral neuropathy (DPN), providing a disease-modifyng treatment. These data corroborate the results already observed in patient with DPN (Polydefkis M et al *Brain 2004;127:1606- 15*; Khoshnoodi M et al *Ann Clin Transl Neurol 2019;6:2088-96*) with the novelty of using skin biopsies taken before and after treatment with high-dose capsaicin to painful feet. The authors' hypothesis of a regenerative ability of capsaicin via a reversible chemical axotomy of cutaneous nerve terminals is of great interest as well as the suggestion of a priming effect of the baseline ongoing regeneration in DPN. However, the number of patients is too small and the population heterogeneous to allow the identification of characteristics that may contribute to the effects of the capsaicin 8% patch on nerve regeneration. Next studies should be set to detect the "responders" to this treatment through a stratification by age, duration and severity of diabetes/neuropathy and capsaicin dosage. However, these results bring already hopeful perspectives for the treatment of both PDPN and diabetic foot syndrome.

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Reference. Anand P, Privitera R, Donatien P, Fadavi H, Tesfaye S, Bravis V, Misra VP. Reversing painful and non-painful diabetic neuropathy with the capsaicin 8% patch: Clinical evidence for pain relief and restoration of function *via* nerve fiber regeneration. Front Neurol. 2022 Oct 26;13:998904. doi: 10.3389/fneur.2022.998904. PMID: 36388188; PMCID: PMC9643187.
https://www.frontiersin.org/articles/10.3389/fneur.2022.998904/full