

Topical analgesia is a viable option

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Commentary

The last 2 decades more and more attention has been given to topical analgesia. Peripheral nerves in the epidermis are innervated by topical analgesics with the aim to reduce neuropathic pain. Systemic side effects are rare, because the purpose of topical analgesics is not to penetrate deeper than the epidermis. Thus topical analgesics are particularly beneficial in the treatment of geriatric patients with high risk of undesirable side effects, drug interactions and altered metabolism due to intake of multiple medications. Even high concentrations of active compounds in topical analgesics do not give rise to serious side effects, such as ketamine cream up to 20% [1]. The absence of severe side effects most probably resides in the fact that the skin has its own metabolism for xenobiotic molecules [2]. Metabolism of ketamine occurs through various cytochrome P450s enzymes (CYP2B6, 2C9, 2C19, 3A4, 2A6, and 3A5), which are present in the epidermis [2].

Ketamine is mainly an N-methyl-D-aspartate (NMDA) receptor antagonist. NMDA receptors are peripherally present on sensory axons and keratinocytes [1,3]. Activation of these receptors results in mechanical allodynia and hyperalgesia, and ketamine can dampen this overactivity [1]. A double-blinded cross-over randomized clinical trial showed this dampening effect of topical ketamine in patients with complex regional pain syndrome (CRPS). In 18 CRPS type I and 2 CRPS type II patients topical ketamine 10% significantly reduced allodynia evoked by lightly brushing, as well as hyperalgesia evoked by skin prick [1,4].

An important factor to achieve an analgesic effect through topical analgesics is probably the integrity of the sensory nerves, with the preservation of the signal transduction from the skin to the brain. An elegant double blind study made this idea compelling, in which the effect of topical clonidine 0.1% compared to placebo in painful diabetic neuropathy (n=179) was examined [5]. After 12 weeks of treatment there was no statistical difference between the active and placebo group in pain scored on the 11-point numerical rating scale (NRS). But when the groups were stratified according to the function of the nociceptors, tested before the treatment with capsaicin 0.1%, interesting results revealed. The more burning patients experienced after capsaicin 0.1% application, the more statistically significant and clinical difference between the groups was present.

Analgesic cream could be used directly for testing instead of capsaicin 0.1%. In our experience the onset of action of topical analgesics is within 30 minutes [6]. The patient can thus directly give notice whether a specific topical analgesic has a pain reducing effect or not.

Another important factor which might blur the effect of a topical analgesic is the negative symptom of neuropathic pain: no signal transduction. This negative symptom is often experienced as numbness, tightness, 'walking on clouds', or as 'a wooden shoe'. The positive symptoms of neuropathic pain are due to overactivity of the nerves and are experienced as tingling, pins and needles, stabbing, burning, painful cold and itch. Topical analgesics can only reduce the positive symptoms. When a topical analgesic has reduced positive symptoms, negative symptoms usually become more pronounced. The feeling of numbness or tightness can be so disturbing, that patients still score high on the NRS when measuring pain. Thus distinction in measurement of negative and positive symptoms is essential. A double blind study (NCT00471445) to evaluate amitriptyline 4% and ketamine 2% in chemotherapy induced polyneuropathy patients (n=458) indicated this important distinction. A composite score of negative and positive symptoms, numbness and tingling, was used as the primary endpoint. After 6 weeks no statistical difference was seen between the active and placebo group. Thus, when tingling is reduced, numbness will be more pronounced and the composite score of these two symptoms will stay the same.

Characterizing neuropathic pain to evaluate the effect of a topical analgesic can be done through questionnaires such as the neuropathic pain symptom inventory (several neuropathic pain symptoms scored on the NRS). Educating patients that topical analgesics can only reduce the positive symptoms, though not the negative symptoms is necessary for an optimal treatment.

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