Cutaneous Anesthesia in Neuropathic Pain: Systematic Analysis

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Abstract

This review is based on an idea that the administration of local anesthetics to the skin for the treatment of neuropathic pain can result in different types of analgesic effects depending on the presence or absence of skin anesthesia. There are many reviews on topical local anesthetics that provide pain relief without skin anesthesia, the aim of this review is to analyze studies on neuropathic pain treated with cutaneous anesthesia. The reference list of 369 articles was reduced to 8 publications that met inclusion criteria (presence of anesthetic effect was a requirement). The large magnitude of pain relief and the high consistency of the positive outcomes were commonly reported. With the single skin anesthesia treatment, both separately and collectively, the reviewed publications reported that more than half of the patients had complete pain relief, often lasting much longer (days or weeks) than the anesthesia. However, because the number of reviewed articles is small, and they represent single case reports or case series, no reliable conclusion could be drawn. The question merits investigations designed to provide high strength of evidence.

Keywords: Chronic pain; Infiltration anesthesia; Neuralgia; Skin infiltration; Skin patch; Subcutaneous infiltration; Topical anesthesia

Introduction

Over the past 50 years a number of attempts have been made to use skin infiltration with local anesthetics for the treatment of herpes zoster and postherpetic neuralgia (PHN) [1]. Usually, these regimens were combinations of the local anesthetic skin infiltrations with the addition of corticosteroids. With the appearance of various topical formulations of local anesthetics, adequate anesthesia of unbroken skin became an attractive alternative to skin infiltrations [2]. There are a number of publications on the effect of topical lidocaine in neuropathic pain, especially in PHN. However, the therapeutic effect of topical lidocaine was observed without cutaneous anesthesia. For example, though Lidocaine Patch 5% does not suppress sensation to light touch or pin-prick, it does provide “slight to moderate” pain relief in PHN [3-5]. The recently published study by Kromova et al. convincingly demonstrated that the effects of the patch on sensation are minimal [6]. The Campbell commentary for this aticle suggested that the often disappointing clinical effects of the patch might be because of “underdosing” [7].

It is possible that the administration of local anesthetics to the skin for the treatment of neuropathic pain can result in the different types of analgesic effects depending on the presence or absence of skin anesthesia. When skin anesthesia is provided (by skin infiltration or using topical local anesthetics in adequate concentrations), the analgesic effect beyond the duration of anesthesia is different from that observed without skin anesthesia (lidocaine patch). There are many reviews on topical local anesthetics that provide pain relief without skin anesthesia, the aim of this review is to analyze studies on neuropathic pain treated with cutaneous anesthesia.

This review is designed to determine the ability of cutaneous anesthesia provided by infiltration or topical administration of local anesthetics, to produce relief of neuropathic pain lasting beyond the duration of anesthesia; and to evaluate the effectiveness of treating neuropathic pain with repetitive inductions of skin anesthesia. We reviewed studies on the treatment of neuropathic pain with local anesthetics infiltrated intra- or subdermally. Studies with topical local anesthetics were included only if there was a specific confirmation of an anesthetic effect.

Methods

A comprehensive literature search was conducted using Medline (1966 – January 2011), Embase (1980 – January 2011), and book chapters. Only articles published in English were collected. The list of identified articles was reviewed to find potentially eligible studies.

Inclusion criteria

All types of original reports were reviewed; including observational studies, case series, and single case reports evaluating the treatment of neuropathic pain with local anesthetics infiltrated intra- or subdermally and with skin anesthesia induced by topically applied local anesthetics. Studies with the topical anesthetics were included only if there was a specific indication confirming the presence of anesthetic effect of a topical formulation.

Exclusion criteria

Interventions excluded were neuraxial blockades, sympathetic neural blockades, and blockades of specific peripheral nerves. Pain syndromes excluded were migraine, complex regional pain, herpes zoster of less than 3 months duration, visceral pain, pain of malignancy, and acute postoperative pain.

Keywords

According to the type of skin treatment: “Skin anesthesia”; “Cutaneous anesthesia”; “Dermal anesthesia”; “Infiltration anesthesia”; “Skin infiltration”; “Subcutaneous infiltration”; “Topical anesthesia”; “Topical application”.
Table 1: Criteria of methodological quality assessment for case reports or case series. 

| Criteria                                      | Score |
|-----------------------------------------------|-------|
| 1. Clinical history provides critical information |       |
| 2. Target problem appropriately identified    |       |
| 3. Design allowed for the examination of cause-and-effect relationship |       |
| 4. Blockade was confirmed by sensory changes (sensitivity to pinprick, touch, etc) |       |
| 5. Adequate baseline measurements              |       |
| 6. Number of treatment visits ≥ 1             |       |
| 7. Individual data from pre-treatment and post-treatment phases |       |
| 8. Statistical analyses of the multiple measurements made during pre-treatment, treatment, and post-treatment phases of the case |       |
| 9. Replication of results in other patients presented in the article. |       |

*mostly based on Tate et al. [8]

Discussion

Our search has revealed only case reports or case series; these articles represent the category of research publications with low-quality evidence [38,39]. However, taken together, these reports have two common features important for the assessment of evidence: the large magnitude of the effect and the high consistency of the reported outcomes. The magnitude of effect observed in the evaluated reports should be graded as large, especially in publications with the single skin anesthesia treatment. Both separately and collectively, the reviewed publications reported that more than half of the patients had complete pain relief, often lasting much longer than the anesthesia. The consistency of results is also impressive: all articles reported complete pain relief in more than half of the patients.

The articles with a series of skin treatments include 2 reports [31,34] on lidocaine skin infiltrations and one report [37] on topical administration of EMLA cream. The skin infiltrations included mostly weekly treatments and produced relief of pain in facial neuralgia (complete relief lasting for months in all 4 patients) [31] and in various PHN (good results in 5 and fair in 3 of 10 patients) [34]. Topical application of EMLA cream, described in the third study, provided only hypoesthetic, not anesthetic effects: tactile and pain thresholds increased by only 15-20%. This might explain the absence of any significant effect on the intensity of pain in PHN despite a decrease in the frequency of intermittent attack [37].

The topical application of local anesthetics on intact skin has a major limitation – poor penetration through epidermis. To overcome this problem, combinations of various approaches are usually applied: the addition of different chemical penetration enhancers including isopro-
Local anesthetics applied to the skin topically or by infiltration will inevitably be systemically absorbed. Therefore the contribution of the central effects of local anesthetics to the therapeutic outcome in neuropathic pain should always be considered [51,52].

This systematic review is subject to certain limitations. Publication bias cannot be ruled out: it is possible that negative trial results were not published [53]. As a result, there is the possibility that our findings will skew positive. The reviewers of the articles were not blinded with respect to sources of the publication. However, the methodological criteria used for the articles assessment were strict; in addition, all articles independent of their quality score reported positive outcomes. Most importantly, due to the unsystematic nature of the clinical observations presented in this review, no reliable conclusion can be drawn concerning the effectiveness of skin anesthesia in neuropathic pain. However, two features of the analyzed reports are important in the large magnitude of effects and the high consistency of the positive outcomes.

Thus, our analysis reveals discrepancy between mostly positive results published in the literature and low quality of evidence in the studies presenting these results. It indicates that the accumulated data has reached the level when the questions on the effectiveness of skin anesthesia in neuropathic pains merit investigations designed to provide high strength of evidence. The results of such investigations will provide the answer to the question posed recently by Campbell – "Could more anesthesia lead to more pain relief" [7].

References

1. Bonica JJ, Buckley FP (1990) Regional analgesia with local anesthetics. The Management of Pain. (2nd edn), Philadelphia.
2. Eidelman A, Weiss JM, Lai J, Carr DB (2005) Topical anesthetics for dental instrumentation: a systematic review of randomized, controlled trials. Ann Emerg Med 46: 343-351.
3. Rowbotham MC, Davies PS, Verkempinck C, Galer BS (1996) Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. Pain 65: 39-44.
4. Davies PS, Galer BS (2004) Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia. Drugs 64: 937-947.
5. Khalil W, Alam S, Puri N (2007) Topical lidocaine for the treatment of postherpetic neuralgia. Cochrane Database Syst Rev 16: CD004846.
6. Krumova EK, Zeller M, Westermann A, Maier C (2012) Lidocaine patch (5%) produces a selective, but incomplete block of Ad and C fibers. Pain 153: 273-280.
7. Campbell JN (2012) Commentary: How does topical lidocaine relieve pain? Pain 153: 255-259.
8. Tate RL, McDonald S, Perdices M, Togher L, Schultz R, et al. (2008) Rating the methodological quality of single-subject designs and n-of-1 trials: introducing the Single-Case Experimental Design (SCED) scale. Neuropsychol Rehabil 18: 385-401.
9. Secunda I, Wolf W, Price J (1941) Herpes zoster: local anesthesia in the treatment of pain. N Engl J Med 224: 501-503.
10. Dan K, Higa K, Noda B (1985) Nerve block for herpetic pain. Advances in Pain Research and Therapy. New York.

Multiple neurobiological mechanisms underlying neuropathic pain have been suggested, and treatment of pain by targeting specific mechanisms has been advocated [44]. It was hypothesized that lidocaine delivered through intact stratum corneum, even at concentrations that do not suppress sensory functions, can still produce pain relief by reducing spontaneous and evoked activity of abnormally functioning afferents [45]. In the PHN and other neuropathies, damaged cutaneous nociceptive fibers in the areas of pain may have abnormal spontaneous activity; such activity can be relieved by membrane stabilization induced by local anesthetics [46]. Table 2 lists possible mechanisms of pain relief produced with or without skin anesthesia. Some must be similar in both situations (see points 1 and 2 in the table) [45,46]. However, there are a number of mechanisms that can operate only with skin anesthesia. All of them are related to the propagation of sensory impulses from the area of pain (see points 4-6) [47-50]. Block of all sensory input from the skin might explain the similarity between the effect of skin anesthesia and the effects of major nerve blocks, including relief of neuropathic pain by blocks distal to the site of nerve lesion [43].

**Table 2:** Possible mechanisms of pain relief provided by skin infiltration or topical administration of local anesthetics.

| Mechanisms | With skin anesthesia | Without skin anesthesia |
|------------|----------------------|-------------------------|
| 1 Decreasing excitability of abnormally sensitized but intact sensory receptors in the skin [45] | + | - |
| 2 Inhibiting ectopic neural discharge in damaged afferents of the skin [46] | + | - |
| 3 Inhibiting ectopic neural discharge in primary afferents outside the skin (due to axoplasmic transport or systemic absorption) [46] | ± | ± |
| 4 Blockade of the propagation of pain signaling discharge (originated in intact or damaged nerve afferents in the skin) [47] | + | - |
| 5 Blockade of all sensory input from the area of pain projection: pain cannot be projected and, therefore, felt [48] | + | - |
| 6 Elimination of fiber interaction cross-talk or sensory inflow imbalance [49,50] | + | - |
| 7 Elimination of central sensitization maintenance from a peripheral focus [44,48] | a. by inhibiting impulse generation | + | - |
| b. by blockade of impulse propagation | + | - |

Possible mechanisms of pain relief provided by skin infiltration or topical administration of local anesthetics.
11. Stadthner DA (1986) Xylocaine treatment for acute herpes zoster. Hosp Pract (Off Ed) 21: 16-21.
12. Stow PJ, Glynn CJ, Minor B (1989) EMLA cream in the treatment of post-herpetic neuralgia. Efficacy and pharmacokinetic profile. Pain 39: 301-305.
13. Galer BS, Rowbotham MC, Perander J, Friedman E (1999) Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain 80:533-538.
14. Devers A, Galer BS (2000) Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study. Clin J Pain 16: 205-208.
15. Katz NP, Gammahtorin AR, Davis MW, Dworin RH (2002) Lidocaine patch 5\% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. Pain Med 3: 324-332.
16. Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC (2002) The lidocaine patch 5\% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. Clin J Pain 18: 297-301.
17. Meier T, Wasner G, Faust M, Kuntzer T, Ochsen F, et al. (2003) Efficacy of lidocaine patch 5\% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. Pain 106: 151-158.
18. Argoff CE, Galer BS, Jensen MP, Oplea N, Gammahtorin AR (2004) Effectiveness of the lidocaine patch 5\% pain on qualities in three chronic pain states: assessment with the neuropathic pain scale. Curr Med Res Opin 20: S1-S28.
19. Hempenstall K, Nummikko TJ, Johnson RW, AHern RP, Rice AS (2005) Analegesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med 2: e164
20. Wasner G, Kleintert A, Binder A, Schattnerreder J, Baron R (2005) Postherpetic neuralgia: topical lidocaine is effective in nociceptor-deprived skin. J Neuror 252: 677-686.
21. Hans G, Sabatowski R, Binder A, Boel I, Rogers P, et al (2009) Efficacy and tolerability of a 5\% lidocaine medicated plaster for the topical treatment of post-herpetic neuralgia: results of a long-term study. Curr Med Res Opin 15: 1295-1305.
22. Baron R, Bruxelle J, Rogers P, Hans G, Boel I, et al. (2009) Topical 5\% lidocaine (lincoaine) medicated plaster treatment for post-herpetic neuralgia: results of a double-blind, placebo-controlled, multifacational efficacy and safety trial. Clin Drug Investig 29: 393-408.
23. Baron R, Mayoral V, Lejon G, Binder A, Steigerwald I, et al. (2009) 5\% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polymonopathy: an open-label, non-inferiority two-stage RCT study. Curr Med Res Opin 25: 1663-1676.
24. Wilhelm IR, Tzabazis A, Likar R, Sitti R, Greissinger N (2010) Long-term treatment of neuropathic pain with a 5\% lidocaine medicated plaster. Eur J Anaesthesiol 27: 169-173.
25. Rowbotham MC, Fields HL (1989)Topical lidocaine reduces pain in post-herpetic neuralgia. Pain 38: 297-301.
26. Rowbotham MC, Davies PS, Fields HL (1995) Topical lidocaine gel relieves postherpetic neuralgia. Ann Neurol 37: 246-253.
27. Estanislao F, Carter K, McArthur J, Olney R, Simpson D, et al. (2004) A randomized controlled trial of 5\% lidocaine gel for HIV-associated distal symmetric polyneuropathy. J Acquir Immune Defic Syndr 37: 1584-1586.
28. Kanai A, Kukami C, Niki Y, Suzuki A, Tazawa T, et al. (2009) Efficacy of a metered-dose 8\% lidocaine pump spray for patients with post-herpetic neuralgia. Pain Med 10: 902-909.
29. Kanai A, Segawa Y, Okamoto T, Koto M, Okamoto H (2009) The analgesic effect of a metered-dose 8\% lidocaine pump spray in posttraumatic peripheral neuropathy: a pilot study. Anesth Analg 108: 987-991.
30. Hollander E. (1938) Dependence of sensation of pain on cutaneous impulses. Arch Neurol Psychiat 40: 743-747.
31. Livingston WK (1943) Pain Mechanisms. A Physiological Interpretation of Causalgia and Its Related States. New York: MacMillan.
32. Fowler W (1947) Relief of lightning pains in tabes dorsalis. Br J Vener Dis 23: 90-91.