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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 pinprick, 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

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1. Clinical history provides critical information
2. Target problem appropriately identified
3. Design allowed for the examination of cause-and-effect relationship
4. Block adequacy 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]

Table 1: Criteria of methodological quality assessment for case reports or case series*.

lidocaine"; "EMLA"; "Topical tetracaine"; "Topical etidocaine"; "Topical benzocaine"; "Topical dibucaine"; "Dermal patch"; "Skin patch"; "Anesthetic patch"; "Anesthetic gel"; "Anesthetic spray"; "Anesthetic cream"; "Anesthetic ointment". Terms added to the name of a specific treatment were "Neuropathic pain" OR "Neuralgia" OR "Chronic pain".

The electronic and manual search of literature identified 369 articles. The results of this initial search after reviewing the titles and abstracts were reduced to 30 articles, which were read in their entirety. Because all included articles can be classified only as case series or single case reports, the scale for assessment of methodological quality of the reports was based on case study design [8] modified to include 9 items (Table 1). Study quality was defined by the number of fulfilled validity criteria. Studies were scored based on a maximal possible score of 9 criteria as 100%.

Results

The search identified 30 reports as possibly relevant, 22 of which were excluded after the review [3,9-29]. Eight reports met inclusion criteria [30-37]. Most of the excluded reports are related to the topical administration of lidocaine. Thirteen of them are studies with Lidocaine Patch 5% or 5% Lidocaine Medicated Plaster with confirmed absence of skin anesthesia ("skin sensation to light touch and pinprick are preserved") [4]. Five studies with other formulations of lidocaine and one with EMLA were also excluded because of the absence of any evidence of anesthesia. Of the reports with local anesthetic skin infiltrations, two were excluded because the effect of skin infiltration was assessed only in acute herpes zoster, and one was excluded due to the absence of separately presented results on skin infiltration (mixed together with the results on blockades of large peripheral nerves).

Articles included in this review can be classified as single case reports or case series; there were no well-designed randomized, blinded studies. Pain syndromes included PHN, tic douloureux, and neuralgias due to tabes dorsalis, trauma, or nerve entrapment. The most commonly used local anesthetics for skin infiltration were lidocaine and procaine; lidocaine and EMLA were used for topical anesthesia. It was possible to assess the outcome of a single treatment resulting in skin anesthesia in 5 reports, and 3 reports gave the outcomes after a series of such treatments. All 5 publications assessing a single skin anesthesia treatment [30,32,33,35,36] reported complete pain relief in all or a majority of patients. Rowbotham and Fields [35] observed "essentially complete" pain relief in 7 of 12 patients. In 3 of the patients this relief produced by a single infiltration lasted from 1 to 4 weeks. Kissin et al. [36] reported that skin anesthesia induced by topical applications of lidocaine resulted in complete pain relief in 4 of 5 patients. These authors also observed that complete pain relief outlasted the duration of skin anesthesia; in 2 patients it lasted 7 days and in 2 other patients 18 and 24 hours. Overall, the total number of patients in all 5 reports with single-treatment assessment was 23, 17 of whom had complete pain relief.

Three articles reported the results of series of skin treatments [31,34,37]. Livingston [31] reported on 4 patients with facial neuralgias treated with a series of 3 or 4 procaine (2%) infiltrations during a 3-week period. The treatment resulted in a complete pain relief lasting 5-6 months in 3 patients and 6 weeks in one patient. Ogata et al. [34] used a series of mostly weekly lidocaine (1%) infiltrations for treatment of ten patients with PHN; the authors concluded that the treatment was effective in 5, fair in 3, and not effective in 2 patients. Attal et al. [37] studied the effect of EMLA cream in 11 patients with PHN. EMLA (5g) was applied to the area of maximal pain under an occlusive dressing for 5 hours daily for 6 consecutive days. Thirty minutes after 5-h EMLA application, tactile and pain thresholds (measured with von Frey filaments) were increased by approximately 15-20%, demonstrating slight hypoesthesia, not anesthesia. This hypoesthesia did not persist at the 12^{th} hr after the last (6^{th}) EMLA application. The authors did not observe any significant effect on continuous pain following single or repeated applications of EMLA. However, a series of EMLA applications reduced the number of painful intermittent attacks (from 6.4 to 3.8 per day, $p < 0.01$) and the intensity of brush-induced allodynia (by 20-50%, $p < 0.05$).

The articles' quality scores vary from 94% to 39% (of the highest score possible for the assessment of the methodological quality of case study design [8]. There appeared to be no relationship between the quality of the articles and their outcome: all articles independent of their quality score reported positive outcomes.

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-

pyl alcohol, propylene glycol, glycerol, dimethylsulfoxide, or one of 275 other compounds [40]; the use of physical enhancers such as occlusive dressing, or heating the skin; other approaches include the use of eutectic mixtures, liposomal encapsulations, etc. Various local anesthetic formulations based on these approaches have different degrees of success in providing acceptable rate of drug penetration. A 2-5% lidocaine solution with isopropyl alcohol and glycerol (chemical enhancers) under occlusive dressing provided complete skin anesthesia one hour after application [36,41]. However a Lidocaine Patch 5% has a minimal effect on sensation [4,6]. The effect of EMLA cream on skin sensitivity is very variable, from slight hypoesthetic effect to complete anesthesia, depending on the duration of application, site, and the completeness of the occlusion [42]. Thus the effects induced by various topical formulations of local anesthetics can be quite different: in some cases they elicited cutaneous anesthesia like that seen with local anesthetic skin infiltration and in other cases they do not.

Pain in PHN can be relieved with or without skin anesthesia. The difference is in the degree of pain relief, its duration, and underlying putative mechanisms. The reviewed articles revealed that pain relief with skin anesthesia is complete in more than half of cases. In addition, the relief can last for days, weeks, or sometimes months after the treatment, similar to what was reported in many cases with major nerve blocks [43]. Without skin anesthesia, the effect is "slight or moderate." For example, Rowbotham et al. [3] observed a decrease in pain intensity of 12 mm (mean VAS score) from 49 mm preapplication level. To maintain pain relief without skin anesthesia, topical lidocaine should be applied daily for up to 12 hours.

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 nocicepetive 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].

	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	 + +	 + –

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

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].

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