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Differential analgesic effects of subanesthetic concentrations of lidocaine on spontaneous and evoked pain in human painful neuroma: A randomized, double blind study

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HIGHLIGHTS

- Different mechanisms of evoked and spontaneous pain are proposed in neuropathic pain.
- A peripheral drive from the neuroma is required for evoked and spontaneous pain.
- Spontaneous and evoked pain can be differentially modified by local anesthetics in the periphery.
- Central amplification changes in neuropathic pain are temporally related to a peripheral input.
- Painful neuroma is a clinical model of neuropathic pain.

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ABSTRACT

Background: Both peripheral nerve injury and neuroma pain are the result of changes in sodium channel expression. Lidocaine selectively inhibits the spontaneous ectopic activity by binding to sodium channels. Subanesthetics concentrations of lidocaine are able to produce a differential block of the ectopic discharges, but not propagation of impulses, suppressing differentially the associated neuropathic pain symptoms. The aim of this study was to investigate the differences between the analgesic effects of lidocaine 0.5% and a control group of lidocaine 0.1% on several neuroma related pain modalities.

Methods: Sixteen patients with neuropathic pain due to painful neuromas caused by nerve injury participated in this randomized, double-blind experiment. The patterns of sensory changes were compared before and after injection of 1 ml lidocaine 0.5% and 0.1% close to the neuroma, the sessions being 1–2 weeks apart. Spontaneous and evoked pains were assessed using a visual analogue scale (VAS), quantitative and qualitative sensory testing. The primary end-point measure was defined as the change in pain score measured from baseline until 60 min after injection. Assessments of spontaneous pain and evoked pain were done post injection at 15 s, 30 s, 1 min, and at 5-min intervals for the first 30-min post injection and then every 10-min to 1 hr post injection. The assessments of pain were performed between the limbs in the following order: spontaneous pain, then assessment of dynamic mechanical allodynia and then hyperalgesia.

Results: Lidocaine dose-dependently reduced spontaneous and evoked pain scores by more than 80% with maximum effects between 1 and 5 min for evoked pain and between 3 and 15 min for spontaneous pain. While evoked pain normalized rapidly reaching about 50% of the control level 20 min after the injection, spontaneous pain levels continue to be lower in comparison with baseline values for more than 60 min. When comparing the time course of analgesia between spontaneous and evoked pain, lidocaine-induced a greater reduction of evoked pain, but with shorter duration than spontaneous pain. The differences between evoked pain and spontaneous pain were statistically significant in both groups (lidocaine 0.5% group; $p = 0.02$ and lidocaine 0.1% group; $p = 0.01$). Reproducibility was high for all assessed variables. Surprisingly, both lidocaine concentrations produced a sensory loss within the area with hyperalgesia and allodynia: hypoesthesia occurred earlier and lasted longer with lidocaine 0.5% (between 30 s and 5 min) in comparison with lidocaine 0.1% ($p = 0.018$).

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Conclusion: Differential analgesic effects of subanesthetic concentrations of local lidocaine on evoked and spontaneous pain in human neuroma suggest that different mechanisms underlie these two key clinical symptoms. Spontaneous pain and evoked pain need an ongoing peripheral drive and any possible CNS amplification change is temporally closely related to this peripheral input.
Implications: Painful neuroma represents a clinical model of peripheral neuropathic pain that could lead to a significant step forward in the understanding of pain pathophysiology providing the opportunity to study spontaneous and evoked pain and the underlying mechanisms of neuropathic pain. The proposed model of neuropathic pain allows testing new substances by administration of analgesics directly where the pain is generated.

1. Introduction

Partial or complete peripheral nerve injury caused by accidental or surgical trauma often leads to the formation of neuromas resulting from disorganized nerve fibres with axonal sprouting embedded within connective tissue and invading immune cells [1,2]. They are classified based on microscopic injury to "end neuroma" at the proximal end of the injured nerve and "in continuity neuromas" within an injured nerve that has not been totally sectioned, both implying loss of axonal continuity [3]. The regenerative axon sprouts commonly exhibit excessive mechanical sensitivity [4] because of altered membrane properties due to change in sodium receptor expressions [5,6]. Sodium channel isoforms Na(V)1.3, Na(V)1.7 and Na(V)1.8 have been shown to accumulate in chronic painful human neuromas [7]. Altered ion channel distribution therefore can contribute to the development of neuroma-associated pain. Clinical features of neuropathic pain include spontaneous pain, either paroxysmal or ongoing pain and stimulus-evoked pain that may involve different mechanisms [8]. Local administration of lidocaine, a sodium channel blocker [9] is known to reduce neuropathic pain [10] by reducing the excessive inputs from peripheral nerve injury [11]. Lidocaine administrated at subanesthetic concentrations blocks the spontaneous and ectopic impulse activity in afferent fibres, activity that is mediated by both tetrodotoxin-resistant (TTX-R) and tetrodotoxin-sensitive (TTX-S) sodium channels [12]. Low lidocaine concentrations produce a differential block effective at blocking ectopic discharge or impulse initiation but not axonal propagation of impulses by electrical stimulation [13]. Using low lidocaine concentrations injected close to a painful neuroma it is possible to evaluate analgesic efficacy at doses that do not impair other aspects of normal sensory function. The present study aimed to assess the effects of low lidocaine concentration injected near the injury site on evoked and spontaneous pain and to test the usefulness of this human pharmacological approach in neuropathic pain patients.

2. Materials and methods

This randomized, double-blinded study was performed in accordance with the ethical principles for medical research involving human subjects that have their origin in the updated Declaration of Helsinki and was approved by the Regional Ethics Committee (approval nr: 2010/066 from 2010-04-07) and Medical Products Agency (approval nr: 159:2010/508979). Clinical Trials NCT02300038. The study was carried out at the Multidisciplinary Pain Center and Hand Surgery Clinic at Uppsala University Hospital, Sweden.

2.1. Patients

Patients were recruited by using a postal follow up questionnaire sent to patients having suffered a nerve injury as confirmed during surgery between 2006 and 2010 at the Hand Surgery Clinic. The number of enrolled subjects in this study was 16 patients who fulfilled the inclusion criteria of being 18 years or older, with a history of persistent spontaneous and/or evoked pain (by e.g. touch, movement), who scored an average daily pain intensity of at least 4 on a 0–10 point numerical pain scale (NRS) interfering with daily activities and who had pain of at least 3 months duration. They all had neuromas after upper extremity surgery or other trauma affecting the radial, ulnar, median or digital nerves and were eligible to participate in the study after giving written informed consent. Patients with other conditions that might confound assessment of pain attributed to posttraumatic upper limb pain or any condition/disease that could interfere with the study measurements, such as drug abuse, diabetes, vascular disease, polyneuropathy or psychiatric diseases were excluded.

2.2. Study design

The patients visited the Pain Clinic twice. Oral and written information about the study was provided and informed consent obtained. Demographic data (date of birth, sex, medical and surgical history) were recorded. Information about the patients' assessments and pre-injection assessments were recorded before the injection, including current medication and other (successful or non-successful) treatment attempts especially local anaesthetics. The same investigator (AM) performed all study procedure assessments. All patients were comfortably seated in a chair and were familiarized with the different methods to be used before the start of the experiment. The neuroma was localized by Tinel's sign [14] and when possible (7 patients out of 16), the localization of a neuroma was verified by ultrasound. Tinel's sign is positive when light percussion over the nerve evokes typical intense stabbing or electric shock-like sensations. As a result of the increased mechanosensitivity of damaged peripheral nerves, there is a massive activation of ectopic sensory discharges acting on mechano-sensitive neural pathways [15]. Therefore, the assessments of sensory function were performed before and after drug administration in all the affected limb in comparison with the healthy contralateral limb.

2.3. Administration of study drug

As the injection was expected to be painful we chose a control group of low lidocaine concentration (0.1%) rather than saline in order to avoid unnecessary pain. The patients were randomized by a computer generated random list to receive either 1 ml lidocaine 0.5% (A) or 1 ml 0.1% (B) respectively, injected close to the neuroma. The alternate dose was injected 1–2 weeks later. Low concentrations of lidocaine were chosen in order to achieve a therapeutic effect and to avoid a complete axonal block. Neither the subjects of the experiment nor the person injecting the lidocaine and examining the patient knew the concentration of lidocaine. Lidocaine was diluted (by another person who had access to the randomization list) in sterile saline (0.9%) to a concentration of 0.1% (3.7 mM) or 0.5% (18.5 mM). The assessments were performed under the same