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Original experimental

Acid-induced experimental muscle pain and hyperalgesia with single and repeated infusion in human forearm

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HIGHLIGHTS

- The intensity of acid-induced muscle pain was pH-dependent.
- Hyperalgesia was detected for all the infusions independent of pH level.
- Repeated acid infusion did not induce any different reactions from the first infusion.

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ABSTRACT

Background and purpose: Acid has long been thought to play an important role in the pain process. Animal study showed that repeated acid stimulation induced central sensitization. The purpose of the study is to investigate muscle pain and hyperalgesia evoked by intramuscular infusion of saline at different pH levels, and to compare the effect of a single versus repeated acid infusions.
Methods: Twenty healthy subjects received infusions of buffered saline (pH 5.0, 6.0, and 7.4) into the brachioradialis muscle in a randomized order. Twelve of the subjects received repeated infusions. The subjects rated the pain intensity on visual analogue scale (VAS). Thermal pain sensitivity, and pressure pain threshold (PPT) were assessed in both arm before, during, immediately after, one hour after, and one day after the infusion. A McGill Pain Questionnaire and pain mapping were completed after each infusion.
Results: The pH 5 solution caused significantly higher pain and larger areas than pH 6.0 or 7.4. The local PPTs were significantly decreased (hyperalgesia) during and immediately after infusion of all three solutions. No significant differences were detected between the first and second infusion.
Conclusions: The intensity of acid-induced muscle pain is pH-dependent. All three solutions induced pressure hyperalgesia at the infusion site. Repeated infusions did not induce increased pain or prolonged hyperalgesia as compared with a single injection. Human intramuscular acidic saline infusion could not produce chronic pain model.
Implications: The acid-induced pain model may reflect the early stage responses to tissue injury of clinical conditions. Repeated intramuscular acidic saline injection model of prolonged hyperalgesia in rodents could not be translated into a human for modelling chronic musculoskeletal pain.

1. Introduction

Tissue acidosis has been observed as a regular phenomenon following inflammation, ischaemia, arthritis, cancer, hematomas, and exercise [1–3]. Local tissue pH has been found to drop to 5.4 in purulent exudates, 4.7 in fracture-related hematomas, 5.0–4.0 in bone cancer, and 6.0 in patients with occlusive arterial diseases in the leg [3]. Considering the painful nature of all the conditions above, the high proton concentration might be a significant contributor to the

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associated pain [1,4]. Previous studies also suggest that a strong reciprocal pain potentiating interaction exists between acidic pH and several inflammatory mediators and neurotransmitters, with low pH playing the dominant role [5–7]. The acid-sensing ion channels (ASICs) play an important role in the activation of nociceptors by low pH and thus may serve as potential targets for analgesic drug developing [3,4,6,8–10].

Human and animal studies have shown that acid can induce both transient and sustained pain [3,4,11]. An acid-induced pain model in rats has been proven to be safe and without significant tissue damage by histological biopsy compared with other inflammation or tumour-induced pain models in rodents [11]. Using acid to produce pain in human skin and muscle has also proven safe [12–14]. Primary mechanical hyperalgesia was reported to be observed following the acid stimulation. In spite of the different methods adopted, the intensity of the acid-induced pain is pH-dependent [3,7,13,14]. A previous study including intramuscular acidic stimulation reported that women experienced higher referred pain and exhibited a stronger correlation between local and referred pain than men [13].

Animal studies have reported that repeated intramuscular acidic stimulations induced spinal hyperexcitability with contralaterally spreading hyperalgesia [8,11,15,16]. Local anaesthetics applied to the muscle previously injected with acidic saline could not inhibit the acid-induced contralateral spreading of hyperalgesia [11] indicating a central origin of the phenomenon. However, spreading of pain has not been found after repeated acid injection into the masseter muscle in neither human [12] nor animal studies [17]. Since the results from human research within this field are limited, further studies should be conducted to elucidate the possible central mechanism of acid-induced muscle pain.

The aims of this human study were to investigate: (1) whether acid-induced muscle pain and (2) pressure hyperalgesia were pH dependent; (3) if spreading sensitization could be evoked by repeated versus single injection of acid stimulation; and (4) if there were gender differences in any of the parameters.

2. Methods

2.1. Subjects

Twenty healthy subjects (7 women, 24.3 ± 3.1 years) participated in a three-session study with a single infusion in each session. Further, 12 of the 20 subjects (4 women, 24.1 ± 2.8 years) participated in sessions with repeated infusions. None of the subjects had a history of pain or injuries or medical conditions that could interfere with normal somatosensory functioning. Women in the menstrual period were avoided. The study was approved by the local ethics committee (N 2011-0081) and conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent.

2.2. Experimental protocol

The subjects participated in three sessions; each with a single infusion of buffered saline with one of three different pH levels (pH 5.0, 6.0 and 7.4). The infusions were conducted in random order and with a one-week interval between sessions. Further, 12 subjects received repeated infusions of either pH 5.0 or pH 7.4 solution with a one-day interval between infusions. In each session, neutral phosphate buffered saline (10 ml) was infused into the brachioradialis muscle over 20 min using a computer-controlled infusion pump.

Cold pain threshold (CPT), heat pain threshold (HPT), mechanical pain sensitivity (MPS), and pressure pain threshold (PPT) were assessed before, during, after, one hour after, and one day after the infusion. The pain intensity was rated by means of an electronic visual analogue scale (VAS). A McGill Pain Questionnaire and a pain map were completed after each infusion.

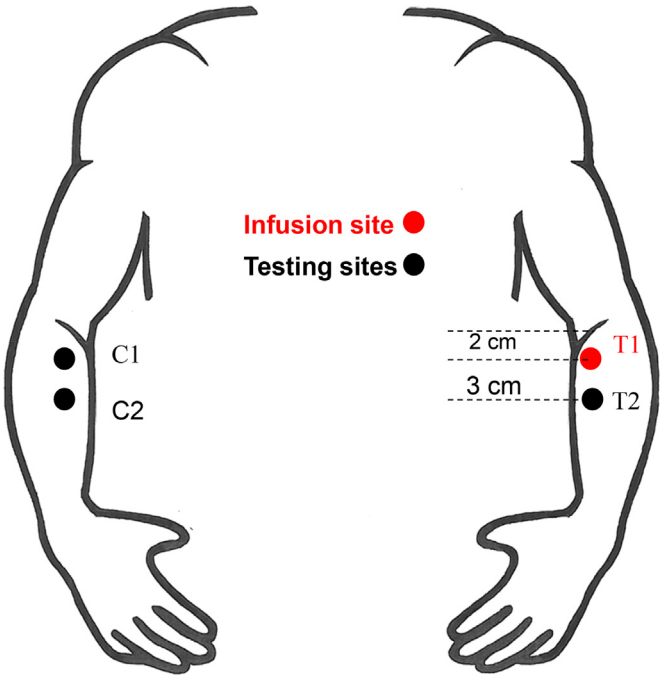

Fig. 1. Infusion sites and testing sites. T1: infusion site on the left brachioradialis muscle; T2: local testing site, 1 cm from infusion site. C1 and C2: testing sites on the contralateral brachioradialis muscle.

2.3. Acidic infusions and pain assessment

The pH adjusted phosphate buffered saline (10 mL, Hospital Pharmacy of Aalborg University Hospital, Aalborg, Denmark) was randomly infused into the left brachioradialis muscle (2 cm from the superior border of cubital fossa) in a double-blinded manner with respect to the pH level. The infusion site was cleaned with alcohol and dried prior to the needle insertion. The needle (27 G, 19 mm, BD Microlance 3, Becton Dickinson, Ireland) was inserted into middle part of the brachioradialis muscle with a depth of 15 mm. The inserted needle was fixed to the skin using surgical tape and sterile cotton. A tube (200 cm, 1.5 ml, G30303M, Care Fusion, Switzerland) was connected to the needle from the syringe. The sterile buffers were infused at a constant rate of 30 ml/h for 20 min using a computer-controlled infusion pump (Asena CC MK-III, Alaris medical systems, USA). The needle and tube were removed immediately after completion of the infusion.

The subjects rated the induced pain intensity on an electronic VAS on which “0 cm” indicated “no pain” and “10 cm” represented “most pain imaginable”. The VAS signal was sampled every 2 s from the beginning of the infusion until the pain intensity had returned to zero. The maximal pain (VAS peak) and the area under the curve (VAS area) were calculated. After the infusion, the subjects were asked to draw the pain areas on an arm drawing describe the quality of the pain on the McGill Pain Questionnaire (MPQ).

2.4. Assessment sites

Two sites in the infusion side and two sites in the contralateral side were assessed (Fig. 1). CPT, HPT MPT, and PPT were assessed 1 cm from the infusion site (T2). All sensory assessments were also conducted at the infusion site (T1) at the same time points except

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