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Specifying the nonspecific components of acupuncture analgesia

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ABSTRACT

It is well known that acupuncture has pain-relieving effects, but the contribution of specific and especially nonspecific factors to acupuncture analgesia is less clear. One hundred one patients who developed pain of $\geqslant 3$ on a visual analog scale (VAS, 0 to 10) after third molar surgery were randomized to receive active acupuncture, placebo acupuncture, or no treatment for 30 min with acupuncture needles with potential for double-blinding. Patients' perception of the treatment (active or placebo) and expected pain levels (VAS) were assessed before and halfway through the treatment. Looking at actual treatment allocation, there was no specific effect of active acupuncture ($P = .240$), but there was a large and significant nonspecific effect of placebo acupuncture ($P < .001$), which increased over time. Interestingly, however, looking at perceived treatment allocation, there was a significant effect of acupuncture ($P < .001$), indicating that patients who believed they received active acupuncture had significantly lower pain levels than those who believed they received placebo acupuncture. Expected pain levels accounted for significant and progressively larger amounts of the variance in pain ratings after both active and placebo acupuncture (up to 69.8%). This is the first study to show that under optimized blinding conditions, nonspecific factors such as patients' perception of and expectations toward treatment are central to the efficacy of acupuncture analgesia and that these factors may contribute to self-reinforcing effects in acupuncture treatment. To obtain an effect of acupuncture in clinical practice, it may therefore be important to incorporate and optimize these factors.

1. Introduction

It is well known that acupuncture may have a pain-relieving effect [32]. It is, however, less clear to what extent specific factors (eg, needle penetration), nonspecific placebo factors (eg, expectation of treatment efficacy), and confounding factors (eg, spontaneous remission) contribute to the reported efficacy of acupuncture [15,20,43]. Recent meta-analyses show equivocal effects of active vs placebo acupuncture [15,42], but moderate effects of placebo acupuncture vs no treatment. This observation suggests that placebo factors may play a role for the observed effect in acupuncture analgesia [7,8,13,18,29].

Because of the apparently large placebo component of acupuncture analgesia, there is a growing interest in specifying these nonspecific placebo factors [3,8,15,43]. Some studies show that patients' overall belief about acupuncture treatment may influence treatment outcome [19,22,43], and one study has directly documented that the perception of the treatment allocation (active vs placebo acupuncture) influences pain levels to a higher extent than actual treatment allocation [3]. Patients' perceived treatment allocation has, nevertheless, never been studied under optimized blinding conditions nor in relation to expectation, which is a key factor in placebo analgesic effects [21,24,27,39,40].

Recently acupuncture needles with optimized practitioner and patient blinding properties have been developed [34–36]. By using these needles, it may be possible to get a less biased understanding

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of how specific and nonspecific factors contribute to acupuncture analgesia. Also, a recent systematic review of expectancy and acupuncture analgesia has called for better ways of assessing expectancy [8]. Most studies use crude measures of expectancy (interviews, questionnaires, or 5-point Likert scales) and turn them into high vs low expectancy [2,5,6,16,17,19,22,31,33]. However, it may be more precise to record expected pain ratings on a visual analog scale (VAS) and compare these to actual pain ratings [21,27,39,40].

Expected pain levels are likely to change throughout the course of acupuncture treatment [8], but so far, to our knowledge, no studies have directly examined this aspect in the context of acupuncture. Expected pain levels have been shown to account for larger amounts of the variance in the late compared to the early phase of pharmacologically active or placebo treatments, thereby suggesting that expectancy may contribute to self-reinforcing placebo effects [10,38,40]. It would therefore be of interest to test the influence of expectancy on pain levels over time after active and placebo acupuncture treatments.

Patients undergoing surgical removal of 1 mandibular third molar were randomized to (1) active acupuncture, (2) placebo acupuncture, or (3) no treatment with acupuncture needles with potential for double blinding [34–36]. The patients' perception of the treatment (active vs placebo acupuncture) was recorded, and the patients' expected and actual pain levels were obtained to answer the following questions:

- Do specific (active minus placebo acupuncture) and nonspecific (placebo acupuncture minus no treatment) factors contribute to acupuncture analgesia?
- Does patients' perception of the treatment (active vs placebo acupuncture) influence the treatment outcome?
- Do expected pain levels contribute to the pain-relieving effect after active and placebo acupuncture, respectively?
- Do expected pain levels account for higher amounts of variance in pain levels in the late vs early phase of the treatment, thereby suggesting a self-reinforcing effect?

2. Methods

2.1. Patients

A total of 111 patients referred to surgical removal of 1 mandibular third molar at the Section of Oral and Maxillofacial Surgery and Oral Pathology, Department of Dentistry, Aarhus University, from September 2008 to July 2009, participated in the study. In order to be included in the study, patients had to have pain due to tooth removal, be $\geqslant$18 years of age, and be in good health, which was defined as risk groups I, II, or III according to the American Society of Anesthesiologists. The indications for surgical removal of 1 semi-impacted mandibular third molar were (1) recurring episodes of pericoronitis ($\geqslant$2 episodes), (2) caries or resorption of the second molar (distal surface), (3) unrestorable caries of the third molar, (4) progressive periodontitis of the second molar (distal surface) or third molar, or (5) other pathologic conditions related to the third molar.

Patients were excluded if they (1) had previous experience with acupuncture, (2) experienced pain < 3 on a VAS (0 to 10) [9] 4 h after surgery, (3) had to take rescue medication during the study period, (4) had a pain disorder that may interfere with the measurement of pain, (5) were medicated 24 h before the experiment, (6) were pregnant or breast-feeding, or (7) had local dental or other medical or psychiatric disorders that prevented them from participating in the study. All patients provided signed informed consent and were compensated with 70€ (500 DKK) for participating in the study. The study was approved by the local ethical committee for the Central Denmark Region (M-20070270).

2.2. Procedure

The study took place at the Department of Dentistry, Aarhus University, Denmark. Before the study, a research assistant (SB) informed the patients about the study and introduced them to the pain rating scales. The surgery started at 9 AM. Immediately after surgery, the patients were asked to rate their pain intensity and pain unpleasantness, after which the experimenter, wearing a white coat, escorted them to an examination room at the research clinic. The patients' pain intensity and pain unpleasantness were monitored every 15 min. No external stimuli other than orange juice and ice cream were allowed during the study. Patients were informed that they would be randomized to 1 of 3 groups: active acupuncture, placebo acupuncture, or a message of no treatment. Patients were then randomized to one of these treatments by drawing a number that corresponded to a sealed envelope containing either of these treatments (treatment group could not be recognized by handling the sealed envelope).

During the treatment, 2 examiners were involved: an acupuncturist and a research assistant. Both were blinded to the type of acupuncture given. In the 2 treatment groups, the patients were introduced to the acupuncturist and invited to lie down comfortably in a horizontal dental chair. The acupuncturist spent approximately 15 min establishing rapport with each patient, inquiring about his or her pain and general well-being. During this conversation, the acupuncturist stated, *"Acupuncture treatment has been shown to effectively reduce pain after surgical removal of mandibular third molars in some patients."*

At the beginning of the treatment (−2 min, ie, right before the treatment was initiated), the research assistant asked the patients about their current pain intensity and pain unpleasantness, and subsequently about the patients' expected pain intensity and pain unpleasantness during the treatment (Fig. 1). At time point 0, the acupuncturist applied the needles in the designated points and rotated the needles manually. Halfway through the study (at 13 min), the research assistant again asked the patients about their current pain intensity and pain unpleasantness, and subsequently about the patients' expected pain intensity and pain unpleasantness levels during the remainder of the session. At the time point of 15 min, the acupuncturist rotated the needles manually. Near the end of the study (28 min), the research assistant asked the patients about their current pain intensity and pain unpleasantness. At the time point of 30 min, the acupuncturist rotated the needles manually and removed the needles.

The period from −2 to 13 min were conceptualized as the early part of the study, whereas the period from 13 to 30 min were conceptualized as the late part of the study, which is in agreement with previous studies [40]. Once the treatment was terminated,

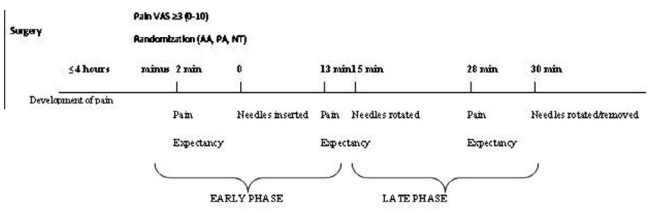

Fig. 1. Experimental design. Patients who developed pain levels of $\geqslant$3 (0 to 10) up to 4 h after surgical removal of 1 mandibular third molar were randomized to receive active acupuncture (AA), placebo acupuncture (PA), or no treatment (NT) for 30 min. Before the treatment (−2 min), halfway through the treatment (13 min), and at the end of the treatment (28 min), actual pain levels and expected pain levels for subsequent time points were measured. Needles were rotated at insertion, at 15 min, and at 30 min when they were removed.