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The Neo-Acu Trial – clinical protocol

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Background:

Newborns and especially preterms in neonatal care are routinely subjected to painful procedures. Pain prevention in these patients is warranted to avoid acute physiologic reactions endangering the neonate (e.g. hypoxemia, drop in blood pressure). [1,2] Furthermore, there are data that repetitive pain experiences in that age group can lead to poorer cognition and motor functions at the age of 18 months as well as to altered cortisol levels at school age. [1,3-5] The actual gold standard for minor painful procedures are orally administered sweet solutions

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with repetitive trials showing positive effects concerning behavioural scores and cry time.[6,7] Nevertheless, recent data suggests that the superficially beneficial effects of orally administered sweet solutions might not reflect the actual state of the nociceptive circuits.[8] In the worst case, orally administered sweet solutions only mask neonatal pain.[8] Therefore, it is questionable if this method could be further regarded as gold standard for neonatal pain prevention for minor interventions.

Therefore, effective, simple to perform and safe methods for pain prevention would be highly valued for neonates and preterms.

Acupuncture proved to have beneficial effects in various trials on pain and other unpleasant symptoms like nausea and vomiting. The vast majority of high quality acupuncture trials were on adult patients[9,10] with very few exceptions.[11-14] When you use needle acupuncture double-blinding is impossible and even single-blinding of the patient seems questionable even with a so-called placebo-needle.[15]

There is to date one publication about the effects of laser acupuncture on skin temperature of neonates coming to the conclusion that there is no attributable endangerment to the neonate.[16] This is in line with safety reports of laser acupuncture.[17]

Aim:

To determine whether active laser acupuncture is more effective than placebo laser acupuncture concerning pain prevention in term neonates undergoing heel lance for routine metabolic screening

Hypothesis:

1. The neonates in the verum laser acupuncture treatment group show an at least 20% lower PIPP score than the patients in the placebo arm

Primary outcome:

Differences in PIPP score between both groups (verum and placebo)

Secondary outcome:

Cry time in seconds (verum versus placebo)

Percentage of participants with a PIPP lower than 6 (indicating pain) (verum versus placebo)

Adverse events

Trial design:

Randomised, placebo controlled, double-blinded trial in healthy term neonates undergoing heel lance for routine metabolic screening

Inclusion criteria:

Healthy term neonate (after completing 37 weeks of gestation)

Age between 2 and 5 days after birth

Parental written informed consent

Exclusion criteria:

Neonates with neuro-developmental disorders

Neonates under concurrent pain medication

Recruitment:

A member of the research team will explain the trial to the parents. All parents of healthy term neonates born at the Saarland University Medical Centre will be contacted to give their written informed consent.

Methods:

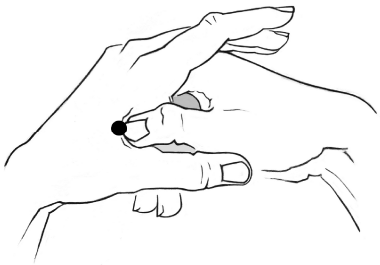
Randomisation is based on computer-generated blocks of 4 (e.g. AABB, ABBA, ABAB). Allocations are stored at the procedure room where the heel lance is performed in continuously numbered sealed opaque envelopes. Immediately before the intervention, the next consecutive envelope will be opened allocating the trial participant to either laser A or B, with one of the devices being the Placebo-laser.

The patients will be treated with a class 3B laser. The laser is a Schwa-Medico Modulas-Handy 2/99, 30 mW, 830 nm, continuous wave, power density 3,8

W/cm2, 1mm laser beam diameter, REF 205237, schwa-medico, Ehringshausen, Germany.

Two superordinate pain preventive acupuncture points (Hegu and Shenmen) will be treated for 30 seconds (0,45J/point) (figure 1).The patient, the acupuncturist and any other person in the room (e.g. parents) will put on protective glasses specific for 830 nm wavelength to avoid retinal damages. For anyone in the room, including the acupuncturist, it will be impossible to differentiate between the active and the placebo laser device. The digital display of both lasers, the visible red guiding light, and the sound emitted during operation are identical, but only one emits an invisible non-thermal infrared laser beam. Thirty seconds after laser acupuncture, a heel lance will be done to collect a blood sample for metabolic screening. Pain reaction, as well as oxygen saturation and pulse frequency will be recorded and pain reactions will be measured later using the premature infant pain profile (PIPP). Therefore, all procedures will be videotaped and evaluated by two independent blinded observers to determine the PIPP. Both investigators will rate all videos independently so that the inter-rater reliability for the PIPP score could be ascertained. Furthermore, the cry time in seconds will be determined using the audio track of the videotapes. No other interventions that could influence the PIPP-score like orally administered sweet solutions, pacifiers, or physical contact is allowed.

Figure 1: Location of the acupuncture points Hegu and Shen Men



Point Hegu or large intestines (LI) 4. On the dorsum of the hand, between the 1st and 2nd metacarpal bones, in the middle of the 2nd metacarpal bone on the radial side.

Shen Men is located on the upper half of the ear near the lateral wall of the triangular fossa

Statistical analysis

From numerous preliminary studies comparing orally administered sweet solutions to no pain prevention, we assumed a mean PIPP score of 8.0 in the placebo group. Based on the assumption that the neonates in the verum acupuncture group would show an at least 20% lower PIPP score than the neonates in the placebo group, 25 patients per group were needed in order to have a 80% power to detect this clinically relevant difference in pain prevention

at a two-sided 5% significance level using a t-test for two independent samples with a common standard deviation of two.

Analysis:

The data will be analysed on an intention-to-treat analysis

Relevance:

Pain prevention in neonates is a major challenge. New data suggest that the actual gold standard (sucrose) for neonatal pain prevention might just only affect behavioural scores without having positive effects on central pain processing making the search for new treatment options even more important. Because laser acupuncture is inexpensive, easy to perform and safe, it will be a good new treatment option for pain prevention in neonates in case of significant effectivity.

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