

A pilot study of ST36 acupuncture for infantile colic

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ABSTRACT

Objective To conduct a pilot study to assess the feasibility of a proposed design of an acupuncture trial to relieve symptoms of infantile colic.

Method An open randomised single-blinded controlled trial, using standardised bilateral treatment of the acupuncture point ST36. Infants fulfilling Wessel's definition of infantile colic were included.

Patients were randomised to active treatment or to no-treatment control. General practitioners (GPs) educated in Western medical acupuncture did the interventions. Parents and GPs' assistants were blinded. Active treatment was the bilateral insertion of 0.20×15 mm Seirin needles to 12 mm depth at ST36. The intervention consisted of daily treatments of 30 s duration for three consecutive workdays. Blinding was done with a red point mark on the skin and circular adhesive dressing covering. The parents were asked two blinding validation questions in the course of the study period. The primary end point was the effect of the intervention assessed as change in crying time per 24 h measured with a crying registration form.

Results The authors improved the standardisation and changed the blinding procedure as a result of the pilot study. Blinding validation questions were considered necessary. The changes made in the main study protocol are discussed.

Conclusion The pilot study led to important changes that were implemented into the final trial protocol. Blinding validation is essential in no-treatment controlled trials of acupuncture on infants, where the parents are blinded assessors of symptom reduction. The authors suggest that blinding validation questions, and the answers to these questions, should be reported.

Clinical Trial Registry Identifier: NCT00907621.

INTRODUCTION

Infantile colic is a painful and insufficiently understood condition in the first months of infancy. The majority of studies of infantile colic have used the definition by Wessel *et al*¹:

Paroxysmic uncontrollable crying and fussing in an otherwise healthy infant under three months of age, with more than three hours of crying per day in more than three days for more than three weeks.

The condition is related to a possible combination of gastrointestinal dysmotility and pain

signals from sensitised visceral afferent pathways in the infant.² No consistent treatment recommendations exist, but moderate effects have been shown by giving sugar water, herbal tea, cow's milk free diet for the nursing mother and cow's milk protein free supplement for the infant.³⁻⁹ Two different studies of children with infantile colic treated with acupuncture versus placebo on LI4 found that acupuncture treatment significantly reduced crying^{2 10} and pain-related behaviour² without noticeable side effects.

Here we describe a pilot and a planned randomised controlled study where Norwegian general practitioners (GPs), who have completed the education programmes of Norwegian Society of Medical Acupuncture (NFMA), use standardised bilateral needling of the point ST36 when treating infant colic. This method is taught in the NFMA teaching programme and is described in the corresponding textbook,¹¹ and is recommended for use. The point is located in the proximal part of anterior tibialis muscle. ST36 is the acupuncture point considered most important for ailments of the gastro-intestinal apparatus in traditional Chinese medicine.¹²⁻¹⁴ A possible neurophysiological mechanism is a beneficial effect on gut dysmotility via parasympathetic vagal reflexes, as well as a centrally opioid-mediated pain inhibitory pathway.¹⁵

In a prospective, multicentre single-blind randomised controlled study, involving 13 GPs' offices throughout Southern Norway, we aim to test the hypothesis that such acupuncture treatment has effect above placebo in infantile colic. We plan to include 100 infants in the acupuncture group and 100 in the no-treatment control group in order to achieve a study strength of 90%, with a clinically relevant difference of 1 h crying time between active treatment and placebo. The main study started in September 2009 and is ongoing.¹⁶ The main study was preceded by a pilot study in order to assess the feasibility of the proposed design of the main acupuncture trial, to validate procedures and to adjust these if necessary. This article describes the lessons learnt from the pilot study and the adjustments done to the original protocol in order to improve internal validity. Problems related to blinding are discussed in particular.

METHODS

The aim of the pilot study was to assess the feasibility of the proposed design of the main acupuncture trial. The pilot study was scheduled with 12 randomised patients. We recruited nine patients during May to August 2009. The parents of these nine infants were informed that they were participating in the pilot study and that it would be open to changes during the course of the study. The results would not be included in the main study. The pilot study was conducted by the two project coordinators of the main ST36 study (HS and TS). Each doctor was assisted by his secretary, and a study manual had been created for the assisting personnel. The data collection was approved by the Norwegian Social Science Data Services (reference 21490/2/JE). The study was approved by the Regional Ethics Committee of South-Eastern Norway, and participants gave informed consent.

Study protocol

Study participants were recruited via information distributed to parents at maternity departments, well-baby clinics and at GPs' offices. The patients fulfilled Wessel's criteria (crying more than 3 h/day, 3 days/week, for more than 3 weeks), were born at full term (defined as >36 weeks) with birth weight >2500 g and should be less than 3 months old at inclusion. There was otherwise no exclusion criteria. The inclusion interview was organised after an initial contact with one of the participating GPs' offices. The GP and assistant assessed inclusion criteria, provided general information and the consent form was filled in. Patients who fulfilled the inclusion criteria were randomised to active treatment or to no-treatment control. The randomisation was done by manual block randomisation by two persons not otherwise involved, and the randomisation was closed until the start of the first treatment. The allocation to treatment or control was concealed in a numbered envelope.

The parents were instructed by the assistant on how to fill in the crying registration form, and the patient was given appointments with the same GP 3, 4 and 5 days after inclusion. The crying registration form had previously been validated in a controlled trial of chiropractic spinal manipulation for infantile colic.¹⁷

The GP was alone in the treatment room with the infant during the intervention. The GP made a mark, 3 mm in diameter, at the point ST36 bilaterally on all children. A water resistant dark red marker was used (Penol 700 Fine Line Permanent, Penol A/S, Copenhagen, Denmark). In the intervention group, an ethylene-oxidised sterile Seirin acupuncture-needle (0.20×15 mm) was inserted at ST36. The point was needled bilaterally to approximately 12 mm depth (figure 1). The two needles were left inserted without manipulation for 30 s while the infant was lying on his/her back on the bench (figure 2). The needles were then withdrawn and a waterproof circular adhesive dressing (Coverplast Barrier 24 mm, BSN Medical GmbH, Hamburg, Germany) was applied (figure 3). The adhesive dressings were changed after each intervention day and were then left attached for 8 days after the last intervention day or until the

adhesive dressing fell off. The infant stayed in the treatment room for 3 min in total, and the parents were called for. An identical procedure, but without the needle insertions, was performed on each infant in the no-treatment control group. The same procedure was performed on days 4 and 5.



Figure 1 The ST36 point marking and inserted needle. The immediate postinsertion erythema is clearly visible in a diameter of 2.2 cm.



Figure 2 The infant lying with inserted needles for 30 s without further manipulation.

The intervention consisted of three treatments of 30 s duration during three consecutive workdays. The parents and the assistant were blinded. The child was not allowed to receive other acupuncture treatment during the follow-up period, but the parents were given no other restrictions in regards to treating their child's symptoms. The parents filled in the crying registration form from the day after inclusion and through the intervention period until the day after the last treatment, as well as 1 and 4 weeks after the last treatment. The assistant conducted a telephone interview 1 and 4 weeks after the last intervention day. The effectiveness of blinding was assessed by asking the parents immediately after the first intervention: 'Do you think the child has received acupuncture or not?' and on day 33, 4 weeks after the last intervention, were also asked: 'Have you noticed any needle insertion marks?'

The primary end point was the effect of the intervention assessed as change in amount of hours crying per 24 h, measured with a crying registration form filled out by the parents. Clinically relevant effect was defined as 1 h difference in crying per 24 h between intervention group and control group.

RESULTS

Nine patients were included in the pilot study. Two of the nine patients withdrew, one before the start of the intervention because of problems with transport, the other after the first treatment day with no reason given. The pilot study thus included seven patients: three in the placebo group and four in the acupuncture group. Mean age at inclusion was 7 weeks; four children were breastfed, one received only milk supplements, one received both and one had data missing. The difference between the acupuncture and the placebo group regarding reduction of crying time from baseline was: 1 day after the last intervention: 87 min. One week after the last intervention: 49 min. Four weeks after the last intervention: 74 min (figure 4). The mean baseline crying time was higher in the acupuncture group than the placebo group, 234 versus 183 min. The percentage difference in reduction in the acupuncture and

placebo groups were 62% and 31% after 1 day, 64% and 55% after 1 week, 79% and 61% after 1 month.

The included numbers are small and not relevant for statistical analysis, but fulfil the clinical relevance criteria of 60 min difference between placebo and acupuncture group at 1 day and 4 weeks after the last treatment day. No adverse events were reported.

All data analyses were carried out using SPSS (Version 18.0.3).

The parents of two out of three children in the placebo group and one out of four in the acupuncture group thought the child had received acupuncture. Thus, the initial blinding procedure of the intervention tended to be valid.

DISCUSSION

This study was undertaken in real life clinical settings, during everyday working hours, where time and compliance by parents and participating GP's are limiting factors. In order to achieve enrolment in the study we had to rely on the parents' proper assessment of crying time during the interview.

This is also a decentralised study where each GP works alone with their assistant. In order to actually give the medical information and answer the medical questions concerning the condition and the study, it is necessary for each GP to meet the parents. We are aware of the potential bias in this decision, but the information procedure is one of strict neutrality once the randomisation had been opened, and the GP takes no further part in the crying registration or interviewing procedures.

The protocol was changed on several points as a consequence of the pilot study. The decision not to include the results of the pilot study into the main study facilitated adjustments of the protocol. The following changes were carried out:

Changes concerning standardisation

1. The original protocol did not specify what time of day to start the crying registration. During the pilot study



Figure 3 The 2.4 cm adhesive water-resistant adhesive dressing covering the point mark and erythema.

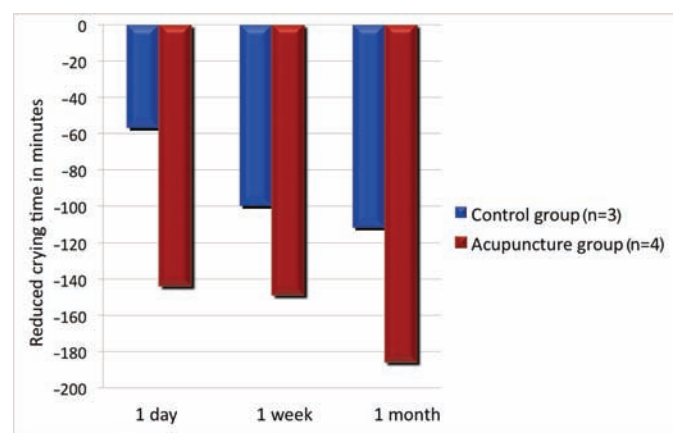


Figure 4 Reduction in crying time in minutes. 1 day, 1 week and 1 month after last intervention day.

we became aware of this standardisation problem. We therefore determined that the crying registration for all participants should start at midnight 2 days before the first intervention day.

2. It became apparent during the pilot study that we lacked a detailed and comprehensive procedure for the actual handling of the infant. We had agreed on the standardised needling technique, but differed in the handling of the child. Non-verbal communication by the practitioner is found to influence outcome in blinded acupuncture studies in adults.¹⁸ We consequently agreed on a detailed level on the non-needling aspect of the handling of the infant, and made a video presentation showing the 3 min handling time on the bench to further facilitate intervention standardisation in the main study of all participating doctors.

Changes concerning blinding

The original blinding method was as follows:

A 3 cm in diameter round marking was made with a dark red water resistant marker, centred in point ST36. This was in order to hide an eventual needle insertion mark and to hide the postinsertion erythema. The water-resistant marking was tested several times and shown to sufficiently hide needle marks and to remain intact through friction and washing of the skin. The tattoo problem also seemed minimal because of the small diameter of the needle, and on skin tests, the pinpricks marks were indistinguishable from the small normal follicular marks sometimes visible as the marking faded.

An adhesive dressing was considered too risky because of accidental or deliberate removing.

The original protocol was set up with the water resistant marking alone. During the pilot study, the mother of one of the infants in the acupuncture group thought she had seen a faint needle mark the day after the last intervention.

We decided on the following changes in the blinding procedure:

(1) We made a point mark at ST36, with the dark red water resistant marker, 3 mm in diameter. (2) Covering the point mark, we applied a waterproof, circular adhesive dressing, 24 mm in diameter. This was changed after each intervention in both groups.

This changes led to additional advantages: the needle insertion was standardised on the same spot each time, the adhesive dressing protected the dark red colour from fading and postinsertion erythema remained covered. The blinding was also kept if the adhesive dressing incidentally or purposely were removed.

The possibility of toxicity of the marker was considered unlikely as the data toxicity sheet for the marker was satisfactory and the small amount of ink on the skin applied once was minuscule. The risk of permanent tattooing was also considered very small as the marker had fast drying ink, the needles were very small in diameter and the ink and needle had been tested extensively on the skin of the project leaders before the start of the study.

The risk of visible needle marks and of postinsertion erythema in the acupuncture group is a possibility in all placebo-controlled trials of acupuncture treatment in infants. Explicit recommendations of reporting of blinding validation in acupuncture trials are not a part of the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines in 2010.¹⁹ There are no reports of parent blinding validation in the two previously published articles on acupuncture in infantile colic.^{2 10} In 1995, Vincent and Lewith proposed a basis for blinding validation questions in acupuncture trials using credibility rating scales.²⁰ Trials investigating non-penetrating sham control use different styles of blinding validation questioning.²¹⁻²³ The possibility of visible needle marks as a blinding problem to be handled in placebo-controlled trials of acupuncture is poorly defined. There are no clear international recommendations on blinding validation in controlled trials of acupuncture treatment in infants. Blinding validation, however, is essential. We suggest that in placebo controlled acupuncture studies on infants, where the parent is blinded and is the assessor of symptom reductions, blinding validation questions should become mandatory, as well as reporting the distribution of answers to the blinding questions.

There are limitations to this study: the reliance of the parents estimation of crying time during the interview as criterion for inclusion might have caused children to be included that did not in fact fulfil Wessel's criteria. The fact that the GP who interviewed the parents was also the one performing the interventions had the potential of bias. The blinding validation questions have not been validated in larger trials and may be imprecise or insufficient. The blinding method of combined red marking and waterproof adhesive dressing has not been validated in larger trials.

CONCLUSION

The pilot study led to important changes that were implemented into the final protocol. A study protocol in larger, blinded, randomised controlled trials of acupuncture in infants may benefit from an open pilot study to facilitate evaluation and implementation of changes in procedures, in order to improve study design and validation. It is especially important concerning the blinding procedure and blinding validation. We suggest that blinding validation questions should be part of the research protocol in no-treatment-controlled studies on infants where the parent is a blinded assessor of symptom reduction. The distribution of the answers should also be reported.

Summary points

- ▶ We planned a randomised controlled trial of acupuncture at ST36 for infantile colic.
- ▶ First we undertook a pilot study to test blinding and feasibility.
- ▶ As a result we were able to improve the trial protocol significantly.

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Competing interests None.

Patient consent Obtained.

Ethics approval Data collection approved by the Norwegian social science data services: 21490/2/JE. Approved by the Regional Ethics Committee of South-Eastern Norway-REK Sør-Øst B: S-08732b 2008/17889.

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REFERENCES

1. Wessel MA, Cobb JC, Jackson EB, *et al*. Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics* 1954;14:421–35.
2. Reinthal M, Andersson S, Gustafsson M, *et al*. Effects of minimal acupuncture in children with infantile colic – a prospective, quasi-randomised single blind controlled trial. *Acupunct Med* 2008;26:171–82.
3. Markestad T. Use of sucrose as a treatment for infant colic. *Arch Dis Child* 1997;76:356–7; discussion 357–8.
4. Lothe L, Lindberg T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double-blind crossover study. *Pediatrics* 1989;83:262–6.
5. American Academy of Pediatrics. Committee on Nutrition. Soy protein-based formulas: recommendations for use in infant feeding. *Pediatrics* 1998;101:149–53.
6. Hill DJ, Roy N, Heine RG, *et al*. Effect of a low-allergen maternal diet on colic among breastfed infants: a randomized, controlled trial. *Pediatrics* 2005;116:e709–15.
7. Hill DJ, Hudson IL, Sheffield LJ, *et al*. A low allergen diet is a significant intervention in infantile colic: results of a community-based study. *J Allergy Clin Immunol* 1995;96:886–92.
8. Swadling C, Griffiths P. Is modified cow's milk formula effective in reducing symptoms of infant colic? *Br J Community Nurs* 2003;8:24–7.
9. Weizman Z, Alkrinawi S, Goldfarb D, *et al*. Efficacy of herbal tea preparation in infantile colic. *J Pediatr* 1993;122:650–2.
10. Landgren K, Kvorning N, Hallström I. Acupuncture reduces crying in infants with infantile colic: a randomised, controlled, blind clinical study. *Acupunct Med* 2010;28:174–9.
11. Heyerdahl O, Lystad N. *Tradisjonell kinesisk akupunktur; dens filosofi og praktiske anvendelse i moderne medisin; lærebok 2*. Trondheim, Norway: Heyerdahl og Lystad ans 2003:310–11.
12. Shanghai College of Traditional Medicine. *Acupuncture: a Comprehensive Text*. Seattle, Washington: Eastland Press 1988:271–2.
13. Deadman P, Al-Khafaji M, Baker K. *A Manual of Acupuncture*. Journal of Chinese Medicine Publications 1998:158–61.
14. Heyerdahl O, Lystad N. *Tradisjonell kinesisk akupunktur; dens filosofi og praktiske anvendelse i moderne medisin; lærebok 2*. Trondheim, Norway: Heyerdahl og Lystad ans 2003:113–14.
15. Takahashi T. Acupuncture for functional gastrointestinal disorders. *J Gastroenterol* 2006;41:408–17.
16. Clinical Trials. Effects of Acupuncture in the Treatment of Infant Colic (NCT00907621). <http://clinicaltrials.gov/ct2/show/NCT00907621?term=NCT00907621&rank=1> (accessed 24 Mar 2011).
17. Olafsdottir E, Forshei S, Fluge G, *et al*. Randomised controlled trial of infantile colic treated with chiropractic spinal manipulation. *Arch Dis Child* 2001;84:138–41.
18. Kelley JM, Lembo AJ, Ablon JS, *et al*. Patient and practitioner influences on the placebo effect in irritable bowel syndrome. *Psychosom Med* 2009;71:789–97.
19. MacPherson H, Altman DG, Hammerschlag R, *et al*. Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *Acupunct Med* 2010;28:83–93.
20. Vincent C, Lewith G. Placebo controls for acupuncture studies. *J R Soc Med* 1995;88:199–202.
21. Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet* 1998;352:364–5.
22. Takakura N, Yajima H. A placebo acupuncture needle with potential for double blinding – a validation study. *Acupunct Med* 2008;26:224–30.
23. Kreiner M, Zaffaroni A, Alvarez R, *et al*. Validation of a simplified sham acupuncture technique for its use in clinical research: a randomised, single blind, crossover study. *Acupunct Med* 2010;28:33–6.

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