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Protocol Title: Development and Validation of a Cloak Shaped Device for Sham Pediatric Tuina

NCT Number: NCT03474172

Protocol Date: April 20, 2018

Version: Version 3 (final)

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Abstract

Background: With the overwhelming acceptance of evidence-based medicine, valid placebo device or placebo procedure become one of the key issues for randomization and placebo-controlled design clinical trials on the validation of treatment modalities. However, few have been developed for Pediatric Tuina (PT) which is a therapeutic massage for children. Blinding both the recipients and the clinical researcher is considered essential for good research practice. Up to now, no well recognized placebo device or procedure for PT has been reported. We developed a Cloak Shaped Device (CSD) , and design a RCT to detect whether the device is effective as a placebo in PT researches.

Methods: This is a two-arm, parallel-group RCT, while participants and researchers will be blinded. Sixty eligible children will be randomly assigned to genuine Tuina or sham Tuina group with the informed consent signed by their guardians. During the process of Tuina, a CSD will be used to cover the children's body so that the children, guardians, observers and researchers will be blinded. Guardians and observers will be asked to ascertain whether they could differentiate genuine Tuina from sham Tuina. The primary outcomes are the accuracy judgment rates based on guardians' and observers' evaluations of the type of Tuina that participants actually received.

Discussion: This study will contribute to the development of a valid placebo device which can be applied in RCTs regarding pediatric Tuina.

Keywords: placebo procedure; device; sham control; Pediatric Tuina; Chinese pediatric massage.

Background

Blinding is one of the important methodological elements in randomized clinical trials (RCTs)based on the principles of evidence-based medicine[1,2].A valid placebo device or procedure may successfully avoid the stakeholders from detecting the group allocation situation[3,4,5].Blinding can minimize the placebo effect as much as possible, therefore the efficacy of the intervention can be evaluated with large extent. Besides, in the trial design, placebo or sham control can not only provide a valid comparator, but also can well control the unknown variables in order to decrease the bias and show the contrasting efficacy of intervention[6].

Placebo has been used in the pharmaceutical clinical trials frequently. In decades, researchers attempted to develop valid sham controls for non-pharmaceutical therapies in Chinese Medicine (CM),including acupuncture[16][17][18], moxibustion[19] and cupping[20].However, in trials adopting non-pharmaceutical interventions, the placebo or sham-therapy have yet been well recognized. Difficulties in the development of placebo devices or placebo procedures of non-pharmacological regimens may occur when participants have had similar experiences[7,8], or when the placebo procedure is not rationally established, expectation bias may easily be introduced[9]. Therefore, to develop appropriate devices for sham massage or sham Tuina is warranted.

PT is a form of traditional Chinese medicine(TCM) therapy in which trained practitioners manually stimulate specific acupoints of the body which are located primarily on the fingers, palms, arms, head, abdomen and back. It has been a valuable option for children’s health promotion since more than one thousand years ago (652 AD) and it is still widely used nowadays in the prevention or treatment of various kinds of pediatric diseases, such as diarrhea, dyspepsia, pneumonia[15]. Although some studies showed that PT is effective with few side effects[12,13,14]. More rigorous designed trials are needed to evaluate the efficacy of PT. The main obstacle in this field is to develop a valid placebo device or procedure which can make the sham Tuina comparison possible. In this study, we will evaluate the validity of a newly developed Cloak Shaped Device (CSD)for sham PT.

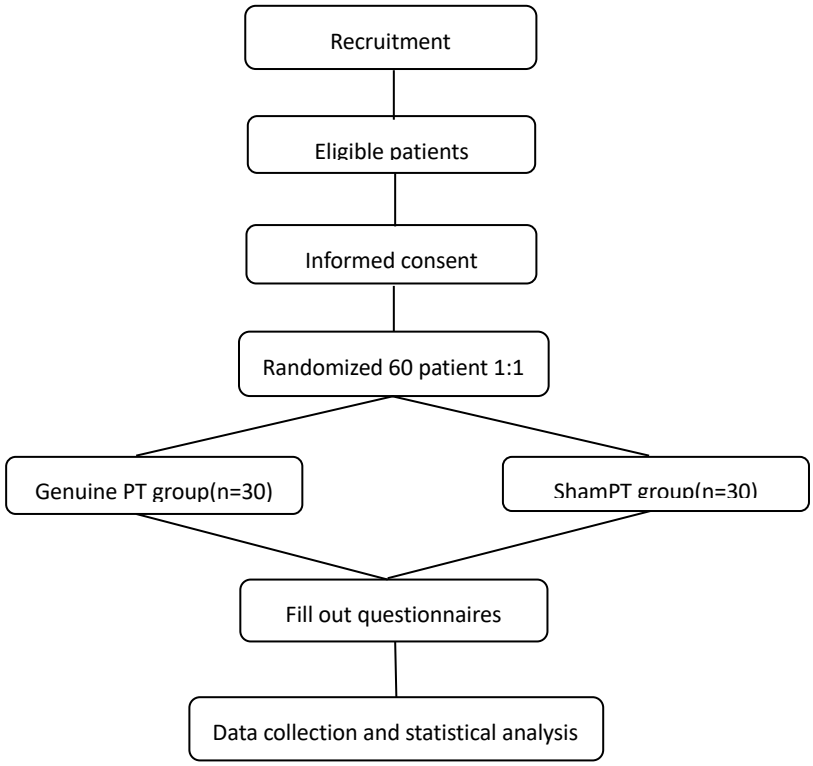
Methods

Study design

We will use the randomized controlled design to assess the validity of the CSD for sham PT. The primary outcomes are the accuracy judgement rates based on guardians' and observers' evaluations of the type of Tuina that participants actually received.

One of the guardians for each child will be informed with all the information of the trial before the child is included. They will be told that their children may receive genuine PT or sham PT. Once the informed consent signed, eligible children will be randomly assigned to genuine PT or sham PT group with 1:1 ratio. Computer generated randomization lists will be concealed in the opaque envelopes, which performed by irrelevantly authorized expert from the department of medical statistics of The 2nd Affiliated Hospital of Guangzhou University of Chinese Medicine.

Trained practitioners will manually do 15 minutes session of Tuina on each participant while the guardians and observers are watching. The guardians and observers will be required to record their judgements of the type of Tuina, either it is genuine or sham PT, that the participant actually received. If the child is equal to or older than 3 years old, researchers will ask the child some questions in terms of the experience of Tuina after they finish the Tuina procedure.



Study population

Children will be recruited at the outpatient department of pediatrics in Dongguan Kanghua hospital which is a tertiary A western medicine hospital located in Dongguan, Guangdong province, China.

Inclusion criteria:

- Children with disease in Pediatric Outpatient Department of Kanghua Hospital
- Children aged 0-6 years.
- Guardian and child can be cooperative over the study period.
- Guardian signed the informed consent.
- Children have no attendance in other studies simultaneously.

Exclusion criteria:

- Child with one or more PT experiences on arms, abdomen or back.
- Child with a previous history of convulsion.
- Child with any of the following conditions on the area to be manipulated: phlebitis, open wound, fracture and tissue damage.
- Child combined with any of following conditions: disorders of consciousness, seizures or twitching, shock, varicella, hand-foot-mouth disease, encephalitis B, and etc.

Sample size

The aim of this study is to evaluate the validity of CSD whether it may have a balanced accurate rate (e.g. 50%) on the type of Tuina that the child actually received in the genuine or sham group, when judged by guardians and observers, respectively. About 95% of the subjects can distinguish the genuine and sham pediatric Tuina accurately without placebo device in the clinical practice. Based on the results from the previous similar researches, an ideal blinding device will be considered have

a good blinding effect while the accurate rate of subjects (genuine group or sham group) on guessing the Tuina type is50%. Therefore, we adopt the single-sample test in the software of PASS 11.0 (NCSS LLC) to calculate the sample size, and set accurate rate of subjects with 95% in non-blinding status, and 50% in blinding status, powered by 90%, and significance levelwith0.05.After the calculation, 24 subjects of each group are needed, on account of the 20% subject may drop out, the finally sample size is 60 subjects in total with 30 subjects in each group.

Development of the CSD

The CSD is made of opaque cotton cloth in cloak-shape. It is big enough to cover the upper body, including upper limbs and trunk, of a child who is 6 year-old or under old. Two narrow holes are present for therapists to insert their hands through and perform Tuina. The entire manipulation process will be covered by the CSD. Blinding will be maintained during the whole study process.

Genuine pediatric Tuina and sham pediatric Tuina

All the techniques and acupoints will be the same in both group, the only difference is that on whose skin that the manipulation will be performed. For Genuine PT the manipulation will be performed on the children's skin directly. However, in the Sham PT group, the therapist will put their own hand above the same skin areas as those in the Genuine PT group and do the Tuina with the other hand of their own. Five acupoints located on the upper limbs and the trunk are involved in both Tuina group, including Neibagua, Banmen and Dachang on hands, Fu on the abdomen, and Qijiegu on the sacroiliac region. The frequency of the techniques are as normal with 150 times per minute for Neibagua, 200 times per minute for Banmen, Dachang, and Qijiegu, 80 times per minute for Fu. The acupoints, manipulation time and frequency are the same for all subjects in two groups. All manipulations will be carried out with light, fast, and soft touch, and coconut oil will be used to protect children's skin in both groups.

Effective measurements

Primary Outcome Measures

- Accurate judgement rate of the guardians' estimation
- Accurate judgement rate of the observers' estimation

Secondary Outcome Measures

- Verbal Rating Scale (VRS) of parent's attitude towards pediatric Tuina (We use the VRS-4 with the higher score representing the more positive attitude to evaluate the degree of the awareness and reliability of the parents towards pediatric Tuina.)
- VRS of Children's Perception of Pediatric Tuina (Verbal Rating Scale, VRS). (We use the VRS-4 with the higher score representing the more positive attitude to evaluate the degree of the perception of the children equal or more than 3 years old during and after the Tuina.)
  Children equal or more than 3 years old in both genuine Tuina and sham Tuina groups will evaluate their sensation, such as pain, warm, discomfort, itch, et al.
- VRS of Parent's Attitude Towards Pediatric Tuina From the Observers' Perspectives. (Verbal Rating Scale, VRS)(We use the VRS-4 with the higher score representing the more positive attitude to evaluate the degree of the reliability of the parents towards pediatric Tuina from the observers' perspectives.)

- Compliance of guardians and children on three continuous PT therapies. (Verbal Rating Scale, VRS)(We use the VRS-5 with the higher score representing the more positive attitude to follow three continuous PT therapies.)

Ethics

The study will respect the Helsinki declaration. It has been approved by the ethics committee of Guangdong Provincial Hospital of Chinese Medicine(Z2017-212-01) and DongGuan Kanghua Hospital(2018003), and has been registered on the ClinicalTrials.gov (Identifier: NCT03474172)before the recruitment of subjects. Informed consent must be endorsed by one guardian of each child if the child is going to attend the trial. All the participants will receive a bonus for the traffic when they complete the trial.

Statistical analysis

All the data in this study will be recorded in a case report form (CRF). When the trial is complete, data will be entered into the database by double entry method. We will use Wilcoxon rank sum test analysis for abnormal distribution data, Mann-Whiney U test for ranked outcomes and chi-squared test for binary outcomes.

In the primary outcome, we will calculate accurate judgment rates on type of Tuina the participants received by guardians and observers, respectively.

In the secondary outcomes, Mann-Whiney U test will be used for the comparison of Verbal Rating Scale (VRS) of parent's attitude towards pediatric Tuina, VRS of Children's Perception of Pediatric Tuina, VRS of Parent's Attitude Towards Pediatric Tuina from the Observers' Perspectives, Compliance of guardians and children in terms of three continuous PT therapies between groups.

Simple Kappa Coefficient will be used to analysis the agreement of the judge results and the attitude towards PT between the guardians and observers. We will use Chi-square test to identify the influence factor, including the education level, age, Children's Perception, parent's attitude, et al.

Statistical Packages of Social Sciences (SPSS) for Windows version 18.0 (Chicago, IL) will be used to conduct the analyses. For all tests, two-tailed P value less than 0.05 is considered as statistically significant.

The Kappa coefficient ranges from 0 to 1.0. In the study, we define if the coefficient value is less than 0.2, it presents that the agreement is slight. If it ranges from 0.21-0.40 indicates the agreement is weak; ranging from 0.41-0.60 means the agreement is moderate; ranging from 0.61-0.80 implies the agreement is favorable. And for those range from 0.81-1.00 it represents that the agreement is perfect.

Quality monitoring

All the researchers will be trained before the trial conducted, including the communication skills with guardians and children, subjects screening, randomization and evaluation procedure. Meanwhile, three experienced therapists will receive a well-designed session of manipulation technical training course to reach a high level of standardization. Detail information on dropout, adverse event of subjects will be recorded on the CRF. During the study period, supervisors will check the CRF aperiodically.

Discussions

To our knowledge, this trial is the first study aiming for the validity of a placebo device in regards of sham PT. On the basis of a rigorous randomized controlled design of our study, the results may provide

evidence for CSD on whether it is worthy to be applied as a useful placebo device for the evidence-based researches of pediatrics when PT or other similar massage interventions will be adopted.
Despite PT, other non-pharmaceutical therapies of Chinese Medicine have developed some sham or blinding methods, such as several types of sham acupuncture or sham cupping devices. The effects of these methods have been revealed by adopting similar research design as this study[16,21-23].
PT has been found to be easily accepted by children based on the light and gentle technique with good safety record. Up to now, none severe adverse event due to PT was reported, some mild adverse events such as skin abrasion can be easily avoided with clear and correct operating instructions. Therefore, guardians and children are very likely to have good compliance to complete the trial. We assume children less than 6 years old cannot differ the genuine PT and sham PT when they are lack of former experience of PT, and consequently the placebo effect for both groups will not be generated systematically. In this case, guardians' and observers' judgements will be more important than children's own perspective in the validation evaluation of the CSD.
In conclusion, this trial may provide valuable evidence on placebo device for the future RCTs in terms of PT or other similar kinds of massage.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Review Board at the Kanghua Hospital in Dongguan, Guangdong province, China (February 6, 2018) and Guangdong Provincial Hospital of Chinese Medical in Guangzhou, Guangdong province, China(January 12,2018). Signed informed consent will be needed for each participant by one of their guardians.

Trial status

The study initiates to recruit on May 2018, and plans to complete before 30 December 2019.

Funding

The National Key Research and Development Program of China (2018YFC1706006)； Clinical Pathway Project of Guangdong Provincial Hospital of Chinese medicine, China(2015, No.119).Science and Technology Research Project of Guangdong Provincial Hospital of Chinese Medicine, China(YN2015QN13);

Competing interests

The authors declare that they have no competing interests.

Abbreviations

RCT: randomized controlled trial; PT: Pediatric Tuina; CM: Chinese Medicine; CRF: case report form. CSD: cloak shaped device

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