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Effect of Hf-rTMS on rehabilitation of chronic pelvic pain syndrome under different intensities : study protocol for a randomized controlled trial.

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Abstract

INTRODUCTION:

Chronic pelvic pain syndrome (CPPS) is one of the most common concentrated pain conditions in urology and gynecology. Nearly one in seven women of worldwide suffer from CPPS each year. CPPS often requires a combination of treatments. An increasing number of studies have shown good therapeutic effects of rTMS on CPPS, however there is a lack of a reasonable treatment intensity reference.The main objective of this trial is to observe the effect of high-frequency rTMS at different intensities on CPPS.

METHODS AND ANALYSIS:

In this prospective, double-blinded randomized controlled trial of outcome assessment, a total of 63 female CPPS participants will be recruited and randomized (1:1:1) to high intensity rTMS, low intensity rTMS, and routinely treatment control group. The control group will be received a ten-day course of conventional pelvic floor rehabilitation, including pelvic floor muscle bioelectro-feedback therapy, pelvic floor magnetic therapy, Hydrosun light therapy. On the basis of conventional treatment, participants in the high intensity group will be received 10Hz with 110%RMT for a total of 15000 pulses; participants in the low intensity group will be received 10Hz with 80%RMT with 15000 pulses. Primary outcome includes visual analogue scale (VAS), The Female Urogenital Pain Index (GUPI), Zung self-rating anxiety scale (SAS) and Zung self-rating depression scale (SDS), and secondary indicators of pelvic floor muscle surface EMG will be measured at baseline and after completion of treatment.

ETHICS AND DISSEMINATION:

This study is approved by the Ethics Committee of Bao 'an People's Hospital, Shenzhen, Guangdong Province (approval number: BYL20211203). The results will be submitted for publication in peer-reviewed journals and disseminated at scientific conferences.

TRIAL REGISTRATION: Chictr.org.cn, ID: ChiCTR2200055615. Registered on 14 January 2022, http://www.chictr.org.cn/showproj.aspx?proj=146720.

Background

Pelvic floor dysfunction is one of the five major diseases affecting human health since the 1990s. The evolution of female pelvic floor structure is more special. Pelvic floor ligaments provide cord-like suspension and support for the stability of organs such as uterus, ovary and vesicorectal urethra. Muscular tissues such as pelvic floor muscles generally support internal organs like bridges. Therefore, it is easy to easily affect the whole abdominopelvic region when the disease occurs[1–3]. With the aggravation of women's life and work tasks, the requirements for pelvic floor support are getting higher and higher, and pelvic mechanical imbalance and various triggers promote the occurrence and

development of various diseases. CPPS is defined as pain without a clear cause that persists or intermittently in the lower abdomen for more than half a year, causing great stress to women's physical psychology as well as life and work economy, and according to statistical surveys, only 2–10% of those who can effectively receive treatment receive outpatient diagnosis[4]. The impact of the disease on women is reflected in emotional anxiety and depression in addition to pain, a decrease in quality of life, and abnormal aspects of physical sensitivity.

CPPS manifests as many peripheral symptoms, and there is studys shows that chronic pain involves systemic pain system dysfunction, chronic pain patients with CPPS have a reduced pain threshold, peripheral receptors may be due to factors such as reduced number of epidermal nerve fibers and increased nerve growth factor synthesis. The brain inhibition and excitability of patients with chronic pain are unbalanced, long-term pain continuously transmits pain sensitizing inhibitory substances such as glutamate through the spinal cord conduction bundle, which increases the level of such substances not only in cerebrospinal fluid but also in key pain processing areas, while the level of excitatory analgesic substances such as opioid peptides decreases[5]. All of these affect the occurrence and development of central sensitization and are the result of physiological plasticity and persistent changes in the central nervous system[6, 7].

The central nervous system functions to regulate excitation and inhibition, and the prefrontal cortex is a key region involved in the regulation of slow-moving pain and cognitive processing [8, 9]. In fact, studies have confirmed the mechanism by which central regulation is feasible [10], and imaging evidence has demonstrated that the long-term effects of chronic pain can cause gray matter density changes in regions such as the primary somatomotor cortex, primary somatosensory cortex, hippocampus and left amygdala [11].

Even these changes are not only related to pain production, but the occurrence of depression is significantly correlated with right hippocampal weight, but also the duration of pain, such as symptom duration of less than 7.5 years was significantly related to left amygdala [12, 13]. After receiving rTMS stimulation, the increase in motor cortex excitability also brought a significant analgesic effect, which was able to increase the concentration of glutamate and glutamine, and biochemical tests demonstrated that glutamate and glutamate in areas such as the prefrontal cortex of CPPS[14, 15]. The change of glutamine concentration has a negative correlation with pain threshold[16], and M1 is related to the pain level of normal people and patients with pelvic pain, and has a positive correlation with pain threshold, which may be related to the fact that M1 is mostly involved in pain loop [17, 18].

Therefore, in the treatment programs known to be commonly used in CPPS (including myofascial manipulation, bioelectric feedback therapy, medium and low frequency electrical stimulation, aerobic exercise and traditional Chinese medicine therapy, etc.) [19, 20], the treatment idea of central regulation from cortical targets worth a try[21, 22]. RTMS stimulates the brain area within two centimeters of the scalp, can trigger descending inhibitory neural pathways to act at the level of the dorsal horn to reduce

chronic pain, can change neuronal activity, and affect the cerebral cortex associated with pain perception, such as the prefrontal cortex, primary somatosensory cortex, etc[23, 24].

The allodynia and hyperalgesia of the cortical projection pain areas of the pelvis in CPPS patients suggest that dysfunction of the central pain system may be at the heart of the disease[25, 26]. Paresthesia and pain occur due to pelvic floor dysfunction. As the pain persists, systemic changes in the central nervous system occur, and the central nervous system remains in a state of high activity, showing disruption of pain regulation and enhanced central sensitization processes.

Nowadays, rTMS is considered as a safe and non-invasive brain stimulation technique. Based on the above mechanism, it has been proved that rTMS can regulate the central lesions caused by chronic diseases by inhibiting and reversing neuronal sensitization[17, 27, 28]. Transcranial magnetic technology recommends the left prefrontal cortex as a target in treatment guidelines applied to chronic pain, i.e. In 2012[29], when rTMS was first used to treat pelvic and perineal pain, Louppe et al performed four-week rTMS stimulation with high-frequency 100% RMT in two female patients with average pain for more than 7.5 years by stimulating the M1 area, and the patients had a continuous improvement in pain and an improvement in quality of life during three weeks of treatment and follow-up. In subsequent studies, high-frequency stimulation of 110%[30] and 80% RMT[31] was used as a more reliable option for treatment, and in mechanistic studies, different intensities were indeed considered to bring different efficacy, however, the effect size was not uniformly positively correlated with intensity. This is also seen in the summaries of the literatures available at present that, in the studies of 80% RMT and 110% RMT, 80% RMT stimulated the improvement of disease symptoms, but the pain reduction was not obvious. These summaries also received the deviation caused by different disease subtypes and intervention implementation. Therefore, we believe that it is necessary to design a randomized controlled trial to more objectively and specifically explain whether the treatment at different intensities will have different effects on the disease development of CPPS.

We hypothesized that the treatment effect of rTMS on CPPS is different at different intensities, the effect of the low-intensity group should be different, and compared with the conventional treatment, the two groups of intervention groups with different intensities are more effective, which can verify the efficacy and safety of rTMS in the treatment of CPPS.

Method/design

Study design

The design of this study is a triple-arm RCT in a 1:1:1 allocation ratio with allocation concealment and assessor blinding. A total of 63 eligible participants will be randomly assigned to the ten high or low intensity transcranial magnetic stimulation (15 min each time, five times a week) or two weeks of conventional pelvic floor treatment group. Results for pain and other symptoms will be assessed at baseline and 2 weeks (at the end of the intervention). All data collectors will be blinded to the group

assignments. The study procedure and outcome assessment schedule for this trial are presented in Figures 1 and Table 1.

Table 1 Schedule of enrolement, assessments and interventions.

	Screening	Pre	2-week Intervention		Post
TIMEPOINT	-1W	0W	1W	2W	+0W
ENROLMENT					
Eligibility screen	×				
Informed consent	×				
ALLOCATION		×			
ASSESSMENTS					
Basic characteristics		×			×
VAS		×			×
GUPI		×			×
SAS		×			×
SDS		×			×
Pelvic floor surface EMG		×			×
Adverse events			×	×	×
INTERVENTIONS					
High-rTMS group			⟷		
Low-rTMS group			⟷		
Control group			⟷		

The x indicates at which point of the trail the respective assessments will take place.

Study population

The study population was women between 20 and 60 years of age (premenopausal) with CPPS. The diagnostic, inclusion and exclusion criteria for the study sample are as follows.

Diagnostic criteria

According to European Association of Urology (EAU) guidelines on chronic pelvic pain (2019 Version) EUA Guidelines on Chronic Pelvic Pain (2019 Update Version), participants with CPPS should have Chronic Pelvic Pain that have no proven infection or other obvious local pathology that explained the pain, often associated with negative cognitive, behavioral, sexual or emotional consequences, with symptoms suggestive of lower urinary, sexual, intestinal, or gynecological dysfunction.

Inclusion criteria

The eligible participants will meet the following criteria: 1. Meet the diagnostic criteria and classification for CPPS in the EUA Guidelines on Chronic Pelvic Pain (2019 Update Version) [32]; 2. Aged 20-60 years old, with a history of CPPS; 3. Gynecological examination and auxiliary examination found no clear pathological changes; 4. Obtain informed consent and voluntarily enter this study; 5. No treatment within 3 months before treatment; 6. Conforming to the habit of right-handed hands.

Exclusion criteria

Patients who meet absolute and relative contraindications for rTMS will be excluded according to evidence-based guidelines for the use of rTMS therapy. The exclusion criteria are as follows: 1. It is contraindicated in patients with acute systemic and intracranial hemorrhagic diseases. 2. Patients with cardiac metal membrane and cardiac pacemaker are prohibited to use; 3. Patients with bleeding tendency: patients with severe heart disease, severe hypertension and severe heart, liver, lung and kidney failure are prohibited; 4. Patients who use implantable electronic devices are prohibited from using them; 5. Patients with intracranial infection or intracranial tumor are prohibited; 6. Patients with intracranial vascular metal stent implantation are prohibited to use; 7. Patients with incomplete vital characteristics and fever are prohibited to use; 8. Those with adverse reactions to magnetic therapy are prohibited to use; 9. Patients with significant changes in blood pressure, heart rate and respiration during treatment are prohibited to use; 10. Open wounds and infections at the treatment site; patients with malignant fluid, active pulmonary tuberculosis and cancer are prohibited; 11. Patients with severe mental illness and epilepsy are prohibited to use; 12. It is prohibited for pregnant women.

Withdrawal criteria and management

Participants will be allowed or required to withdraw from the study based on the following: 1. Those who are unable to continue to receive treatment due to adverse reactions or changes in their condition; 2. Those who do not strictly follow the treatment plan and took other therapies while participating in the study; 3. Those who require to quit by themselves; 4. lost visitors.

Recruitment

Recruitment will be conducted in rehabilitation Department of Shenzhen Bao 'an People's Hospital through online and offline methods such as network, outpatient reception and inpatient medical records screening. Patients at risk of compounding conditions will first be evaluated and screened to determine eligibility for participation based on inclusion and exclusion criteria. Inpatients wishing to participate will obtain their permission and that of the resident, and the research assistant will obtain written informed consent to participate prior to the therapeutic intervention.

Randomization, allocation concealment, and blinding

After baseline assessment, eligible participants will be randomly assigned to high-intensity stimulation, low-intensity stimulation, or conventional treatment. Randomly assigned sequences will be generated

using the PLAN program of SAS V.9.2 statistical software and managed by independent statisticians not involved in recruiting, evaluating, and intervening participants. Eligible participants will be notified by an independent research assistant over the phone of the assignment results. We cannot allow participants, therapists, or attending physicians to be blind to assigned treatment, but outcome assessors and statisticians will be blind to group assignments.

Intervention

Control group

Participants in the conventional treatment control group will not receive repeated TMS in addition to routine pelvic floor rehabilitation. Routine pelvic floor rehabilitation includes pelvic floor muscle bioelectric feedback instrument, pelvic floor magnetic therapy instrument, Hydrosun light therapy. Among them, pelvic floor muscle bioelectrical feedback instrument (French Phenix-USB4) uses ten-minute low-frequency electrical stimulation and 15-minute biofeedback I and II pelvic floor muscle exercises, total 25 min per day; pelvic floor magnetic therapy instrument (Magneuro 60F) uses moderate analgesic high-frequency stimulation for 20 min per day; Hydrosun light therapy (Hydrosun Irradiator 500) uses direct irradiation of the pain site at a distance of 20 – 30 cm for 20 min per day. Conventional treatments will be performed 5 times a week.

High- intensity rTMS group

High-rTMS group will receive high intensity rTMS in addition to conventional treatment. rTMS treatment: CCY 1 stimulator (Wuhan Yiruide) uses, 8-shaped coil focused stimulation was performed, the maximum output was 2.2 T, the coil locates in the center of the left M1 area, placed at a 45 ° inclination from the scalp, the output intensity of 110% RMT will take respectively, 1500 pulses stimulate each time, 10 pulses delivere in each sequence, repeat 150 times, 5 seconds apart, and rTMS treatment will give at 10 Hz for 15 minutes, and the stimulation site is the left primary motor cortex (M1 area). Once a day, five times a week for two weeks and ten sessions for a total of 15,000 stimulations.

Low- intensity rTMS group

The low-intensity treatment group will use the same equipment as the high-intensity group for intervention, but the treatment parameters of the stimulation intensity is 80%RMT, pulse number, interval number and stimulation frequency are consistent with the high-intensity group.

Outcome assessment

The variables include basic information, primary outcome and secondary outcome. Collect basic characteristics at baseline. Primary and secondary outcomes will be measured at baseline and at the end of the intervention period. All primary and secondary outcomes will be evaluated by experienced staff at Shenzhen Bao 'an People's Hospital, who will not be aware of the results of participant allocation.

Basic information

Recruiters will use a self-designed questionnaire to collect participants' demographic characteristics (e.g., gender, age, height and weight, reproductive status) as well as disease and drug use history. Basic visual analogue scale (VAS), The Female Urogenital Pain Index (GUPI), Zung self-rating anxiety scale (SAS) and Zung self-rating depression scale (SDS), will be assessed using the corresponding scales. Baseline measurements will be completed prior to the first treatment.

Primary outcomes

Pain severity uses VAS [33] to be assessment. The VAS is a 100mm line where the "0" end (0) indicates complete painlessness and the other end (10) indicates the most severe pain imaginable. The patient will mark the severity of the pain online. Its simplicity makes it easy to use for pain assessment.

Secondary outcomes

GUPI[34] uses to assess the severity of symptoms in women with urogenital pain, modifies the NIH-CPSI symptom Index to include female-specific pain (vaginal entrance pain, urethral pain, pain during or after sexual intercourse). There are 10 pain items with a total pain subscale score of 0-13, 2 urinary symptom items with a total urine subscale score of 0-10, and 3 QOL items with a total QOL subscale score of 0-12.

SAS[35 , 36] is a norm-referenced scale which enjoys widespread use a screener for anxiety disorders. The scale measures one's mood over the past week with a rough score multiplied by 1.25, with a score below 50 being normal, 50 to 59 indicating mild depression, 60 to 69 indicating moderate depression, and 70 or more indicating major depression. According to previous literature studies, the mood changes of patients with long-term pain are obvious, and self-rating scale can be used to preliminarily distinguish their emotions.

SDS[37] consists of 20 items, divided into 4 self-rating scales, uses to evaluate the subjective feelings of anxious patients within two weeks, the standard score is rough multiplied by 1.25 rounded parts. A final score below 50 is normal, 50-59 indicates mild depression, 60-69 indicates moderate depression, and over 70 indicates major depression [38].

Pelvic floor surface EMG will be collected at baseline and after intervention. EMG assessment will be conducted in the pelvic floor rehabilitation Room of Bao 'an People's Hospital. Participants will be sampled using the Glazer procedure of Med Lander myoelectric pelvic floor biofeedback instrument. Data includes pre-resting phase, variogram 1, rapid contraction phase, rise time, recovery time, slow muscle phase, variogram 2, endurance test phase, variogram 3, post-first ten second ratio, post-resting phase, and variogram 4 [39-41].

Safety measurements

During the intervention, participants will be monitored for the occurrence of adverse events. All participants will be asked about adverse events after each treatment until the adverse events are resolved. Any participant who is found to be at risk to himself or others (suicide, neglect), or who has a serious adverse event will be referred to the relevant clinical services. Any adverse event, including irritation site pain and condition aggravation. Causality will be assessed in relation to the rTMS intervention and the severity of adverse events. Serious adverse events will be reported to the Ethics Committee in 72 hours.

Sample size

According to previous studies[42], when the effect size was 0. 5, β= 0.1 and α =0.05, VAS score will be taken as the main measurement standard and G-Power V3.1.9.2 software was used. The sample size was calculated to be about 16.93 subjects. Taking into account the 20% shedding criteria, each group will include 21 subjects from each group. A total of 63 participants will be required for this study.

Statistical analysis

SPSS software version 26 will be used to analyze the data, and statistical analysis was conducted by independent statisticians. First, the Kolmogorov-Smirnov test is used to determine its normal distribution. If the data is normally distributed, analysis of variance (ANOVA) with repeated measures was used to compare the mean pain scores of each group. A P value less than 0.05 is considered significant. The continuous variable will be expressed as a normal distribution of the mean and SD or a non-normal distribution of the median. Classification variables will be described as frequency or percentage.

Adverse reactions (AEs) will be analyzed using the Chi-square test or Fisher's exact test. If formal statistical analysis between groups is not possible due to insufficient power, AEs is tabulated and summarized using descriptive statistics.

Data collection and management

Data will be collected by an outcome evaluator using a Case Report Form (CRF). The CRF will then transcribe into a password-protected document manager by the research assistant until unlocked at the end of the study.

Patient and public involvement

Prior to the recruitment phase, individual patients and experienced therapists unrelate to the trial recruitment analysis will be invited in the inpatient population to investigate the study design and feasibility of the intervention. Based on their comments, the evaluation method and timing of treatment will be adjusted to avoid interfering with routine treatment arrangements. No patients or members of the public will be involved in recruiting or implementing and measuring the results. The results will be sent to the participants via written reports and email. The burden of the interventions include in this study will not be assessed by the patients.

Ethics and Communication

This study is approved by the Ethics Committee of Shenzhen Bao 'an People's Hospital in December 2021 (BYL-20211203). Any changes to the protocol will be submitted to the Ethics committee for approval. This study has been Registered and can be obtained through the Registration website in China (ChiCTR.org, identified as ChiCTR2200055615. Registered on 14 January 2022). Written informed consent of all participants will be obtained after they have read an information manual describing the project and potential risks and benefits, and if they have any questions to discuss with the investigator. All collected digital data will be stored in password-protected files. Only the data analyst will have access to the data at the end of the trial. The results of the randomized controlled trials will be published in a peer-reviewed journal with undetermined data available in a public repository at the time of publication. The results will also be communicated through scientific meetings. It will follow the standards of the International Board of Medical Journal Editors and will not involve any professional authors .

Discussion

As one of the non-invasive brain stimulation techniques, repetitive transcranial magnetic stimulation has a deeper role than other peripheral regulation techniques [14, 28, 43, 44]. Many studies have summarized that high-frequency repetitive stimulation in M1 area has therapeutic value for chronic intractable pain and generalized pain, and compared with other central regulation techniques, rTMS has been supported by more clinical trial data and has a higher level of evidence [45]. M1-rTMS also has a after-effect effect, and the analgesic effect is maintained for 2–3 days and up to 8 days after a transcranial magnetic stimulation [46], which is why high-frequency M1-rTMS session is more suitable for middle-aged women with recurrent pain attacks without a clear cause and with tight time taking into account work and family.

This study designes for comparison of rTMS of different intensities based on previous literature and clinical studies. One study[47] confirmed that the central region of the response to normal intensity may show no response at levels different from normal intensity (higher or lower), but it is possible that a stimulus increase of as little as 10% May produce significant changes. And, on other diseases such as epilepsy[47–49], schizophrenia and cognitive impairment and other similar conclusions in the experimental study, different intensity of rTMS astrocytes and cerebral blood flow can be adjust different effects, most results suggest strength, the higher the effect is more obvious at the same time, but in the study of Yujuan Ma and others, the best to improve the effect of low intensity. In the studies currently available on the use of rTMS for CPPS or other chronic pain, no uniform parameters (frequency, intensity, or duration) and type of stimulation (transcranial magnetic coil) were used. In some sessions with 80%RMT, the improvement in quality of life, anxiety and depression was not significant. Therefore, we believe it is necessary to design a randomized controlled trial to investigate whether there is a difference in the treatment of this disease with high-frequency rTMS at different intensities.

The emotional and psychological problems of CPPS cannot be ignored [26, 50, 51]. Chronic pain not only causes abnormal changes in pelvic floor muscle strength, but also affects patients' intestinal activity,

urinary system, somatic psychology, quality of life, anxiety and depression. Therefore, we consider it necessary and basic to include pain, urinary outcome, anxiety and depression, and surface EMG in the outcome assessment of this trial design. In conclusion, this study will be the first randomized controlled trial to evaluate the impact of high-frequency rTMS on CPPS at different intensities. It will provide reference for future clinical treatment and research in this direction.

Trial Status

This study is currently in the recruitment phase, with recruitment starting on February 1, 2022 and expected to be completed in September 2022.

Strengths And Limitations Of This Study

- To our knowledge, the first randomized controlled trial of the efficacy and acceptability of different intensities of transcranial magnetic stimulation for CPPS.
- The participants are all patients who come to the hospital with pelvic floor rehabilitation needs, have acceptance of the treatment of gynecological and urological diseases, and the hospital has the corresponding equipment.
- The treatment will be implemented and followed up by the therapist with professional qualification certificate. A total of 63 female participants with CPPS will be enrolled in this prospective assessor-blind, three-arm randomized controlled trial and randomly assigned (1:1:1) to the high-intensity rTMS group , the low-intensity rTMS group and conventional treatment group. It can truly reflect the intervention effect of different intensities of rTMS on CPPS
- In this study, pelvic floor muscle surface EMG acquisition will be performed before and after the intervention. The aim is to investigate the effect of rTMS on neuromuscular bioelectrical activity of pelvic floor muscles after treatment of CPPS.
- A methodological challenge of this study arise will arise from blind implementation and quality control of intervention, and the participant's responsible therapist and physician cannot blindly. In order to minimize performance bias, therapists and physicians in this study will not be involved in recruitment and result assessment or data analysis.

Declarations

Ethics approval and consent to participate

This study is approved by the Ethics Committee of Bao 'an People's Hospital, Shenzhen, Guangdong Province (approval number: BYL20211203). Written informed consent of all participants will be obtained after they have read an information manual describing the project and potential risks and benefits, and if they have any questions to discuss with the investigator.

Availability of data and materials

Not applicable; no data have yet been generated.

Competing interests: None declared.

Funding: None.

Authors' Contributors:

All authors (MYW, RX, JS, CHY, YQZ, XXZ, CCY, ZYW , MW, SJC and HDQ) involve in the study design and approval of the manuscript and MYW, RX and SJC drafte the first version of the manuscript. All authors contribute to drafting the manuscript and have read and approved the final manuscript.

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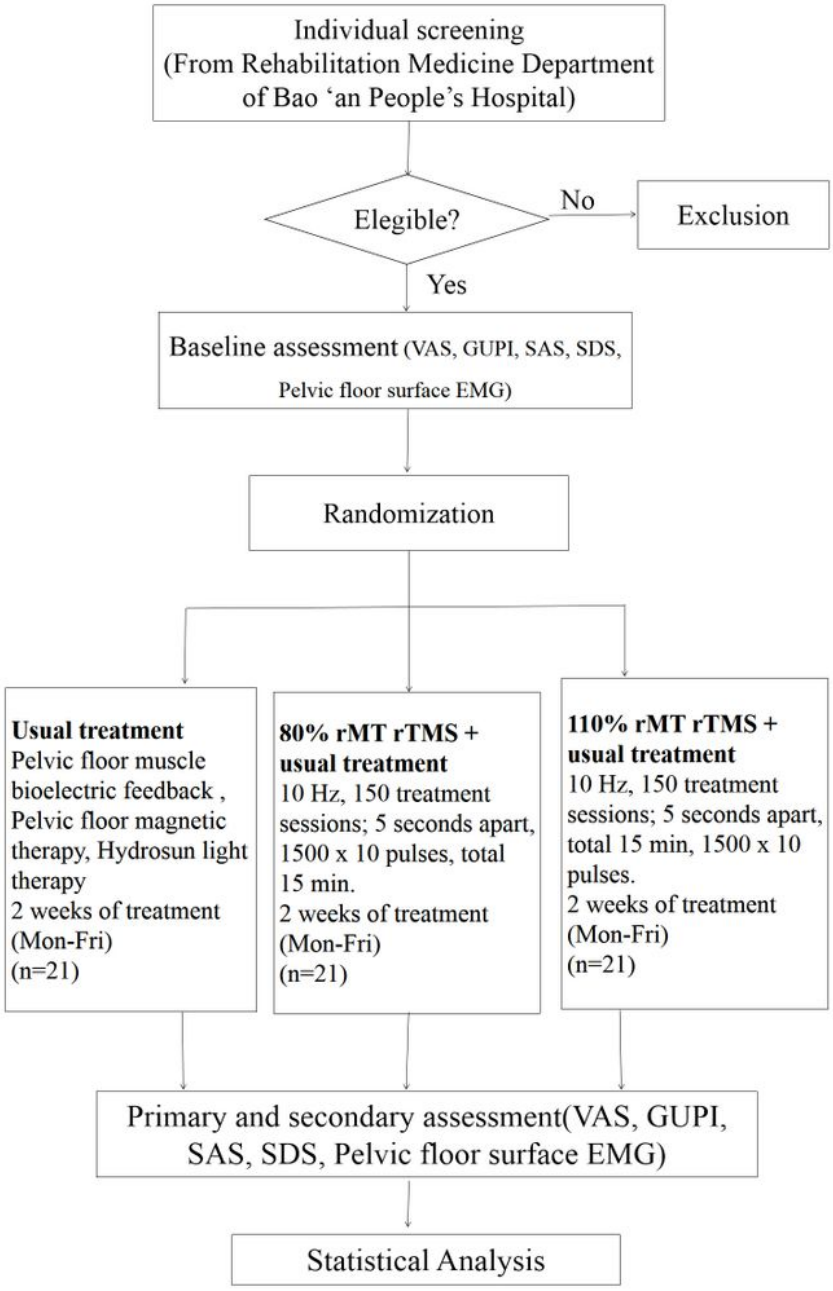
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Figures



* VAS, visual analogue scale ; GUPI, The Female Urogenital Pain Index ; SAS, Zung self-rating anxiety scale ; SDS, Zung self-rating depression scale

Figure 1

Flow chart

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