

Shi's Yi-Qi Bu-Shen Tong-Luo decoction combined with manipulation in the management of wrist stiffness after distal radius fracture

Study protocol clinical trial (SPIRIT Compliant)

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Abstract

Introduction: Wrist stiffness is a common sequela of distal radial fractures. Manipulation is generally used and effective, but problems exist, such as intense pain, swelling during the process of manipulation and long treatment period. Therefore, a combinative therapeutic strategy is necessary to benefit rehabilitation after distal radius fracture. Shi's Yi-Qi Bu-Shen Tong-Luo decoction (BTD) combined with wrist manipulation has been used in the Shanghai Ninth People's Hospital Huangpu Branch in last few decades. BTD has potential therapeutic effects on rehabilitation after distal radius fracture, which should be evaluated by rigorous clinical trial.

Methods/design: A randomized, double-blind, placebo-controlled clinical trial will be conducted to determine the efficiency of BTD in relief of wrist stiffness and pain and function rehabilitation. A total of 80 wrist stiffness patients with or without pain and edema will be enrolled, and treated with wrist manipulation plus BTD or placebo for 4 weeks. The primary outcome measure is the Cooney wrist score. The second outcome measures include pain numerical rating scale, patient rated wrist evaluation, 36-item short form health survey questionnaire, and side effects.

Discussion: Although BTD has shown effects on rehabilitation after distal radius fracture in the Shanghai Ninth People's Hospital Huangpu Branch for decades, the universality of this efficacy needs evaluated. The results of this trial will provide a convincing evidence.

Trial registration: ChiCTR2000029260, January 19, 2020.

Abbreviations: BTD = Shi's Yi-Qi Bu-Shen Tong-Luo decoction, CRF = case report form, DRF = distal radius fracture, PRWE = patient rated wrist evaluation score, SD = standard deviation, SF-36 = 36-item short form health survey questionnaire, TCM = traditional Chinese medicine.

Keywords: distal radius fracture, manipulation therapy, Shi's Yi-Qi Bu-Shen Tong-Luo decoction, traditional Chinese medicine, wrist stiffness

H-Y W and Y-R W contributed equally to this work.

Recruitment will start in March 2020 and is expected to finish in March 2021.

Human ethics approvals were obtained from the Research Ethical Committee of Huangpu Branch, Shanghai Ninth People's Hospital affiliated to Shanghai Jiaotong University (approval number: 2019-Q-026). All participants will provide written informed consent before participating. The purpose, procedures, risks, and benefits of this study will be explained thoroughly to the participants. In addition, the personal information about the potential and enrolled participants will be collected to be used only in this trial, and we will not share the personal information.

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1. Introduction

Distal radius fracture (DRF) is an increasingly common upper limb injury. A certain percentage of complications occur frequently after fracture healing regardless of surgical or conservative treatment. Common complications include wrist instability, stiffness, nonunion, tendon irritation, infection, and local pain syndrome.^[1,2] Wrist stiffness is one of the most common and difficult sequela to treat, up to 30% of DRF patients.^[3] Manipulation is an effective treatment method, but there are problems such as intense pain, swelling and long treatment periods.^[4] Therefore, a combinative therapeutic strategy that could relieve pain, swelling and joint adhesion is necessary to benefit DRF patients after surgeries.

In recent years, traditional Chinese medicine (TCM) has played an important role in the rehabilitation of various kinds of fractures and arthritis. Research suggests TCM has analgesic and anti-inflammatory effects in patients with osteoarthritis.^[5] TCM also could relieve pain and swelling after fractures^[6] and promote fracture healing in multi-regulatory pathways, such as Wnt/ β -catenin, bone morphogenetic protein/Smad and mitogen-activated protein kinase pathway.^[7]

Shi's Yi-Qi Bu-Shen Tong-Luo decoction (BTD) is a century-old historical TCM prescription, including Astragali Radix, Radix Angelicae Sinensis, Flos Carthami, Rhizoma Chuanxiong, Taxilli Herba, Eucommiae Cortex, Epimedii Folium, Olibanum, Stephaniae Tetrandrae Radix (details in Table 1). It has been used to improve joint pain and swelling in the DRF late stage in clinical treatment for decades. According to the TCM theory, BTD could supplement Qi and activate blood circulation, then promote release of adhesion and recovery of joint function.^[8,9] Unfortunately, its efficacy remains unverified with rigorous research and exact data.

Based on this, we propose a randomized, double-blind, placebo-controlled trial to estimate the efficiency and security in managing wrist stiffness of BTD on DRF patients' rehabilitation. This protocol finished in January 5, 2020 (Version 1).

2. Methods/design

2.1. Study design

A prospective single-center, double-blinded, placebo-controlled, randomized clinical trial with 2 parallel arms. The determination of this study is to evaluate the effectiveness and safety of BTD in managing wrist stiffness after DRF. Manipulation by specific therapist is the preliminary treatment, will be used in both

groups. In this study, we will recruit 80 wrist stiffness patients due to DRF from Huangpu Branch, Shanghai Ninth People's Hospital affiliated to Shanghai Jiaotong University.

All participants will be randomized into BTD group or placebo group equal in patient number. Patients in BTD group will receive both BTD (200 mL once, twice a day) and manipulation (30 minutes once, twice a week), while patients in placebo group will receive BTD placebo (200 mL once, twice a day) and manipulation (30 minutes once, twice a week) for continuous 4 weeks. All patients were treated by the same therapist in the entire manipulation.

2.2. Ethical issues

The care provider will invite the patient to participate the trial, tell them in detail why we should take this trial and what kind of rights, obligations and risks they will have if they participate the trials. And the care provider will give them a written informed consent. Only the patients fully understand and sign the informed consent, can they participant the trial. The trial will be conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Research, and the trial protocol has been approved by the Research Ethical Committee of Huangpu Branch, Shanghai Ninth People's Hospital affiliated to Shanghai Jiaotong University (approval number: 2019-Q-026). And the protocol has been listed on Chinese Clinical Trial Registry (ChiCTR2000029260).

2.3. Study participants

DRF participants from the Huangpu Branch, Shanghai Ninth People's Hospital affiliated to Shanghai Jiaotong University will be recruited. Recruitment poster and website advertisements will be publicized. The planned recruitment period is 12 months.

2.4. Criteria

2.4.1. Inclusion criteria. Participants meeting the following criteria will be included.

- (1) patients with diagnosis of DRF and age from ≥ 18 and ≤ 75
- (2) receive conservative treatment (such as plaster external fixation, small splint fixation and external fixation stent) or surgery
- (3) over 6 weeks after the fractures at least, X-ray shows blurred fracture line and well callus growth, external fixation such as plaster and support is removed
- (4) wrist stiffness, with or without swelling, pain, range of joint activities is significantly lower than the healthy side
- (5) able to understand and sign the informed consent and ensure compliance

2.4.2. Exclusion criteria.

- (1) fracture is unstable
- (2) with nerve injury
- (3) abnormal liver and kidney function
- (4) pregnancy, or have no plans of pregnancy, or feeding women
- (5) severe chronic or acute disease
- (6) addictive to alcohol

2.5. Interventions

2.5.1. TCM intervention. In BTD group, patients will be instructed take the 200 mL BTD liquid medicine orally twice a

Table 1

Components of BTD (a separate Word file).

Components of BTD	
Chinese name	Latin name
Huangqi	Astragali Radix
Danggui	Radix Angelicae Sinensis
Honghua	Flos Carthami
Chuanxiong	Rhizoma Chuanxiong
Sangjisheng	Taxilli Herba
Duzhong	Eucommiae Cortex
Yinyanghuo	Epimedii Folium
Ruxiang	Olibanum
Hanfangji	Stephaniae Tetrandrae Radix

BTD = Shishi Yiqi Bushen Tongluo decoction.

People's Hospital affiliated to Shanghai Jiaotong University. Medicine pharmacy will produce the medicinal liquid and paste the sequence number label on plastic bags of BTD or placebo as the list.

The statistician and pharmacy will preserve the randomization list to maintain concealment. And the other investigators will be unable to know the sequence numbers and group of each participant until the trial completed. Medicine with labels will be stored in a locked and individual room. A trained administrator will charge the medicine and the key.

When a participant will be recruited in, the investigator will make a central telephone call and give him/her the medicine (BTB or the placebo) from the administrator.

2.10. Blinding

The staff in the medicine pharmacy only provide drugs, and never participate in the other parts of this study. The investigators, clinicians, therapist, statisticians (analyze outcomes), and participants are unconscious of the group assignment information until the entire trial completed.

2.11. Adverse event

When an adverse event is claimed, we will record it and provide an appropriate treatment. Clinicians will provide emergency services in case of serious adverse events, and report it to the Institutional Review Board within 24 hours. According the condition of adverse event, the blinding might be broken by the co-decision of main trial investigator and leader of ethic committee. Intervention information will be offered by statistician.

2.12. Outcomes

2.12.1. Primary outcome

2.12.1.1. Cooney wrist score (from baseline to week 4). The Cooney wrist scoring system used for the assessment and functional evaluation of the wrist. It includes 4 parts, pain symptoms (25 points), functional status (25 points), grip strength (25 points), range of motion (25 points). The total score of Cooney is 100 points. The higher Cooney score, the better recovery of wrist function. The evaluation criteria is: excellent, 90 to 100 points; good, 80 to 89 points; fair, 65 to 79 points; poor, 0 to 64 points (details in Table 3).

2.12.2. Secondary outcomes

2.12.2.1. Cooney wrist score (from baseline to week 2 and 12). Cooney wrist score from baseline to week 2 and 12 will be calculated as one of the secondary outcomes.

2.12.2.2. Patient rated wrist evaluation (PRWE) score (from baseline to week 2, 4, and 12). The PRWE score questionnaire is designed specifically for evaluation of distal radial fractures that rates wrist function sensitively using a range of questions in 2 parts concerning the patient's pain and function. The PRWE score included 15 items: 5 items related to pain (4 related to the intensity of pain, 1 related to the frequency of pain), 6 items related to special activities, and 4 items related to daily activities which can reflect difficulty in self-care, household activities, work and recreation. Each small item can be marked with a score. The total score is 100, which is calculated by dividing the sum of 10 items scores related to activity and function by 2 (out of 50), plus the total score for the pain subcategory, to give a score on a scale

Table 3

Cooney wrist score (a separate word file).

Functional evaluation	Details	Scores
Pain	No pain	25
	Mild occasional	20
	Moderate tolerable	15
	Severe to intolerable	0
Functional status	Return to regular employment	25
	Restricted employment	20
	Able to work, unemployment	15
	Unable to work because of pain	0
1. Range of motion* (ratio of fracture side to normal side)	100%	25
	75% to 100%	15
	50% to 75%	10
	25% to 50%	5
2. Range of motion* (fracture side from dorsiflexion to palmarflexion)	0% to 25%	0
	120° or more	25
	90° to 120°	15
	60° to 90°	10
Grip strength (ratio of fracture side to normal side)	30° to 60°	5
	100%	25
	75% to 100%	15
	50% to 75%	10
	25% to 50%	5
	0% to 25%	0

* If patients have another normal wrist, we should choose the number 1 evaluation method to score the range of motion of fracture wrist. Otherwise, number 2 evaluation method should be chosen to score it.

of 0 to 100. The higher score, the more severe pain and dysfunction. We enquired patients to fill out the questionnaire based on their wrist pain, special activities and difficulties in daily activities in the past week, and then the specific score was calculated by the doctor to get the final score. The PRWE is the frequently outcome measure available for DRFs.

2.12.2.3. 36-Item short form health survey questionnaire (SF-36) (from baseline to week 2, 4, and 12). SF-36 is an implement for assessing physical status of patients which consists of 36 items in 8 types, including role physical, physical function, bodily pain, vitality, and global health, social function, mental health and role emotional.

2.13. Safety assessments

To assure the safety of participants, the adverse effects will be reported and analyzed. At baseline and after BTB intervention, patients' kidney and liver function will be tested. Additionally, side effects of TCM herbs will be record along the trial, such as gastrointestinal reaction, abdominal pain, dizzy, rash, and and so on. Participants were free to withdraw from the study at any time. The data collection process will be administered by the project director.

2.14. Participant timeline

Recruitment will start in March 2020 and end in March 2021. Last visit will be finished before June 30, 2021. The recruitment process is shown in Figure 1, and the schedule is shown in Table 1.

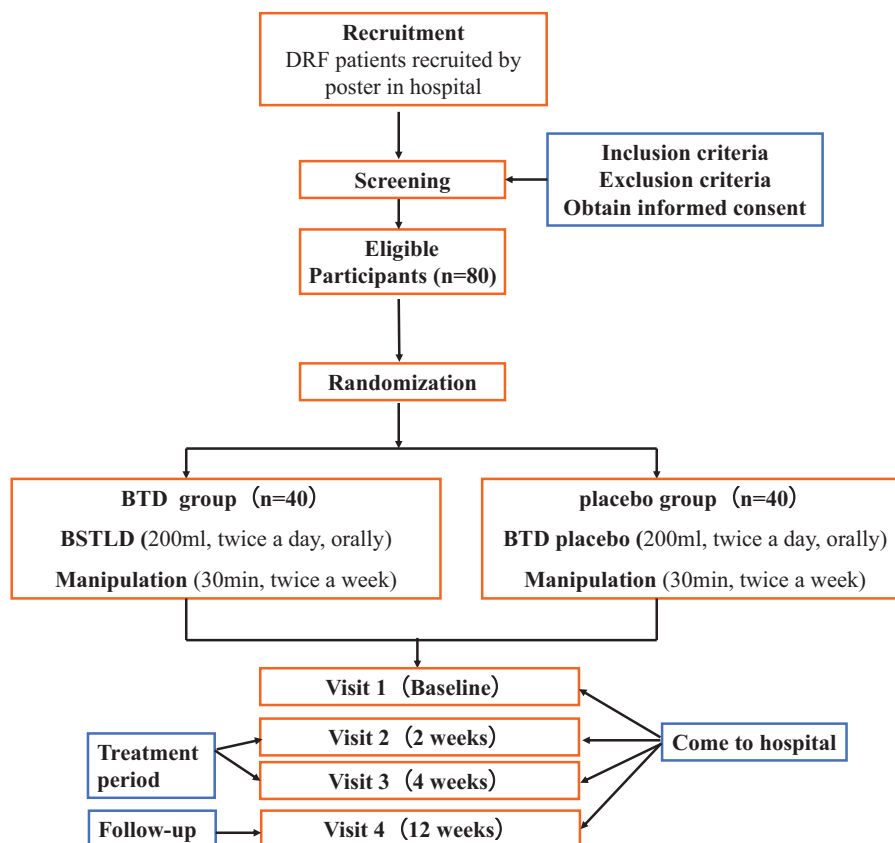


Figure 1. Project overview. BTD=Shi's Yi-Qi Bu-Shen Tong-Luo decoction, DRF=distal radius fracture.

2.15. Data collection and monitoring

All participants will receive treatment of manipulation plus BTD or BTD placebo for 4 weeks and followed-up for another 8 weeks. Two statisticians independently will record 4 rounds of disease assessments (the baseline, week 2, week 4, and week 12) and 2 rounds of safety assessments (the baseline and week 4) in Epidata software (Version 3.1). Disagreement will be solved by discussion with a third statistician.

2.16. Quality control

Huangpu Branch, Shanghai Ninth People's Hospital affiliated to Shanghai Jiaotong University control the quality of this whole search. Training will be conducted to study the process of the entire trial before the trial. All the physicians, therapist and evaluators will receive this training together. A specific investigator will check the CRFs weekly to make sure the study quality.

2.17. Sample size calculation

Sample size was calculated according to the Cooney wrist score, based on previous studies (Zhang et al 2014^[10]). Formula $N1 = N2 = \frac{(Z_{1-\alpha} + Z_{1-\beta})^2 \sigma^2 (1 + \frac{1}{k})}{(\mu_r - \mu_c - \Delta)^2}$ was used, N1 and N2 mean the patient numbers in BTD group and placebo group; $Z_{1-\alpha} = 1.96$ when $\alpha = 0.05$; $Z_{1-\beta} = 1.282$ when $1-\beta = 0.90$; σ (standard deviation of 2 groups) = 7.7; $k = 1$; $\mu_r - \mu_c$ (the difference of Cooney wrist score in BTD and placebo group) = 4; $\Delta = 0$. Therefore, we

decided to include 80 patients in the study (40 of them in each group).

2.18. Statistical analysis

All data analyses will be accomplished using SPSS software (version 24.0). Continuous data are presented as mean \pm standard deviation and categorical data as frequencies. Continuous variables following the normal distribution will be analyzed by Student *t* test; otherwise, nonparametric tests will be used to compare group differences. Statistical test is 2-sided and *P*-value < 0.05 will be defined as statistically significant. We will adopt multiple imputation to handle missing data statistically. A subgroup analyses will be conducted when necessary. Intention-to-treat approach and last-observation-carried-forward method will be applied to deal with the missing values.

3. Discussion

TCM has shown effective in treating fractures and injuries.^[11] BTD consists of Astragali Radix, Radix Angelicae Sinensis, Flos Carthami, Rhizoma Chuanxiong, Taxilli Herba, Eucommiae Cortex, Epimedii Folium, Olibanum, and Stephaniae Tetrandrae Radix. BTD has been used to treat delayed union of fractures and degenerative bone diseases, such as cervical and lumbar disc degeneration, osteoporosis, osteopenia and osteoarthritis.^[12,13] Experimental studies^[14] have found that the TCM formula similar to BTD could accelerate the recovery process after fractures, also could reduce inflammation and swelling of joints

on inflammatory arthritis model mice.^[15] Additionally, experimental study has shown that astragalin, 1 composite of BTB, could attenuate synovial inflammation via MAPKs and AP-1 pathways.^[16]

We use the BTB to treat DRF patients in clinical strategy and this formula works. However, we reviewed the major databases and found no literature to prove that BTB could be benefit to the rehibition of wrist stiffness after DRF.

Based on this, we designed this double-blind randomized controlled trial to explore the effects and safety of BTB. Cooney wrist score is used to evaluate the improvement in pain and wrist motion before and after treatment. The PRWE score measures changes in pain, function and daily life of both physicians' objective assessments and patients' subjective feelings. The SF-36 score is used to assess the physical and mental health of patients, and the safety of BTB is also monitored along the study.

This research will answer whether BTB combined with manipulation is an effective strategy in management of wrist stiffness after DRF. Its positive results will offer patients better functional recovery. Furthermore, clinical physician will have an optional treating strategy.

Author contribution

HYW conduct the trial and draft the manuscript. JHW and PL supervised and coordinated the clinical trial. HYW, GWW, and JG are responsible for recruiting the participants. ZYT is the specific manipulation therapist. All authors read and approved the final manuscript. HYW and YRW conceived of the study and revised the manuscript critically for important intellectual content.

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