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ORIGINAL RESEARCH

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Linggui Yangyuan paste for patients with male infertility: a study protocol for a multicenter, double-blind, double-dummy, randomized controlled trial

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Abstract

Male infertility affects millions of men worldwide and is increasing in prevalence, with asthenozoospermia (AS) and oligoasthenozoospermia (OA) being the most frequent causes, and current treatments are limited. A previous research reported that Linggui Yangyuan paste (LGYY) enhanced sperm viability and motility, but there is a lack of multicenter, rigorous, randomized and controlled studies on its efficacy. Wuzi Yanzong oral solution (WZYZ), a traditional Chinese herbal formula, is one of the most important and first-line drugs for AS and OA in China. We designed a direct comparison of LGYY's effectiveness and safety against WZYZ in treating male infertility, specifically AS and OA. We propose a multicenter, double-blind, double-dummy, randomized controlled trial, which is planned to recruit 162 participants with AS or OA from five centers and will randomize them into two groups, whereby the treatment group will receive intervention with LGYY and WZYZ mimetics, while the control group will receive intervention with WZYZ and LGYY mimetics. The medications will be administered twice daily for 12 weeks, followed by a 12-week follow-up. The primary outcome will be total progressive motile sperm count (TPMSC), and the secondary outcomes will be semen parameters, including semen volume, sperm concentration, total sperm count, progressive motility (PR), PR + nonprogressive motility (NP), Chinese Medicine Symptoms Score (CMSS), spouse pregnancy rate and time to pregnancy. The safety outcomes will be based on the results of routine blood and urine tests, liver and kidney function tests and electrocardiography. Overall, this study aims to provide valuable insights into the potential efficacy and safety of LGYY compared to WZYZ for male infertility (AS or OA), which could guide clinicians to an alternative drug approach to treat patients with AS or OA. This clinical trial is registered at ClinicalTrials.org under the identifier NCT05792813.

Keywords

Male infertility; Asthenozoospermia; Oligoasthenozoospermia; Randomized controlled trial; Traditional Chinese medicine; Linggui Yangyuan paste; Wuzi Yanzong oral solution; Study protocol

1. Introduction

Infertility remains a global health issue [1]. According to the European Association of Urology Guideline on Sexual and Reproductive Health, about 15% of reproductive-age couples worldwide experience difficulties achieving pregnancy within one year of regular unprotected sexual intercourse, and male infertility accounts for approximately 50% of these cases [2–4]. The most common types of male infertility are asthenozoospermia (AS) and oligoasthenozoospermia (OA) [5], and a diagnosis of male infertility has been found to significantly impact men's physical and mental well-being, as well as disrupt social relationships, self-esteem and family harmony [6–8].

Currently, the treatment of AS and OA mainly relies on empirical approaches, such as antioxidants, endocrine therapy and anti-infection treatments [9], and these treatment modalities have their limitations and inefficiencies [10]. In this regard, Traditional Chinese medicine (TCM) is widely used for male infertility due to its unique advantages [11, 12]. Recently, there has been growing interest in using TCM to treat AS and OA [13–15]. For instance, the Wuzi Yanzong oral solution (WZYZ) is a popular TCM formula that has been used as the first-line drug for treating male infertility in China, and

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the Linggui Yangyuan paste (LGYY) has been employed for several years at Xiyuan Hospital (China Academy of Chinese Medical Sciences (CACMS)) to treat AS and OA [16]. LGYY comprises eight herbs, including Lingzhi (*Ganoderma*), Danggui (*Angelicae Sinensis Radix*), Shudihuang (*Rehmanniae Adix Praeparata*), Roucongrong (*Cistanches Herba*), Hongjingtian (*Rhodiolae Crenulatae Radix Et Rhizoma*), Ciwujia (*Acanthopanacis Senticosi Radix Et Rhizoma Seu Caulis*), Tusizi (*Cuscutae Semen*), and Cheqianzi (*Plantaginis Semen*). Although preliminary studies have shown that LGYY has significant advantages in improving the total progressive motile sperm count (TPMSC), existing clinical research is limited to single-center exploratory studies that lack sufficient high-quality evidence to firmly support its clinical effectiveness and safety. Therefore, we designed this present investigator-initiated, multicenter, double-blind, double-dummy, confirmatory, randomized controlled trial to assess the efficacy and safety of LGYY in improving sperm quality for male infertility patients (AS and OA) and its effectiveness in enabling their partners to achieve clinical pregnancy.

2. Methods

2.1 Study design

This multicenter, double-blind, double-dummy, randomized controlled trial conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 [17, 18] and is scheduled from March 2023 to June 2024. We aim to recruit a total of 162 participants from five centers in China and use the block randomization design to ensure an unbiased allocation of participants among the centers, which would be as follows: Xiyuan Hospital, CACMS (n = 54), First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (n = 27), Affiliated Hospital of Shandong University of Traditional Chinese Medicine (n = 27), Chengdu Fifth People's Hospital (n = 27), and Shenzhen Hospital of Traditional Chinese Medicine (n = 27). Participants will be randomly assigned to the treatment or control group in a 1:1 ratio. Each participant will be enrolled only once during the study period. As the herbal paste LGYY and the oral fluid WZYZ have different dosage forms, we have carefully chosen the double-blind, double-dummy design to ensure rigorous blinding and maintain the integrity of the trial's results.

The patients' baseline information will include age, ethnicity, body mass index, smoking and drinking status, disease course, medical history, *etc*. They will receive a 12-week treatment period (evaluation every 4 weeks) and a 12-week follow-up period. A flow chart of the study process is shown in Fig. 1. The enrollment, intervention and evaluation schedules are shown in Table 1.

2.2 Sample size

The sample size is based on the primary efficacy variable, which is the change from baseline in TPMSC at week 12. According to preliminary research, the LGYY group showed a change in TPMSC of $(13.07 \pm 5.17) \times 10^6$, while the WZYZ group exhibited a change of $(10.38 \pm 5.86) \times 10^6$. A one-sided superiority test will be applied for the statistical analysis with a significance level (α) of 0.05 and a power (β) of 0.2, and the participants will be randomized in a 1:1 ratio between the treatment and control groups. Considering the potential lost follow-up rate of patients, estimated to be 20% due to the lengthy trial period and possible participant non-compliance, we have planned to enroll 81 patients per group.

2.3 Eligibility criteria

2.3.1 Inclusion criteria

To be considered eligible for recruitment in this study, the participants must fulfill all of the following criteria [19, 20]:

(1) Meet the diagnostic criteria for male infertility, which include:

① Inability of the female partner to conceive through regular sexual activity without using any contraceptive methods for more than a year due to male factors.

② The female partner should have normal fertility.

(2) Meet the diagnostic criteria for AS or OA.

For AS:

① Sperm concentration should be $\geq 15 \times 10^6$/mL.

② Progressive motility rate (PR) should be <32%.

For OA:

① Sperm concentration should be $<15 \times 10^6$/mL.

② PR should be <32%.

(3) Meet the traditional Chinese medicine (TCM) diagnosis criteria for kidney deficiency and blood stasis.

(4) Aged 22 to 45 years.

(5) Willing to provide a signed informed consent form.

2.3.2 Exclusion criteria

The trial exclusion criteria consist of the following conditions:

(1) Infertility caused by the inability to complete sexual intercourse, including but not limited to erectile dysfunction or ejaculatory disorders.

(2) Infertility due to organic lesions of the reproductive system.

(3) Reproductive system infection, such as chlamydia trachomatis or mycoplasma infection.

(4) Presence of palpable varicocele.

(5) Abnormal and clinically significant levels of sex hormones.

(6) Complications of liver and kidney dysfunction or severe underlying diseases, such as diabetes, cardiovascular and cerebrovascular diseases, mental disorders, malignant tumors or serious organic illnesses.

(7) History of allergy to any drug or ingredients used in the trial.

(8) Receiving other relevant treatments for male infertility within 2 weeks before recruitment.

2.4 Intervention

The treatment group will receive LGYY + WZYZ mimetic, while the control group will receive WZYZ + LGYY mimetic. The LGYY and its mimetic will be provided by the Pharmacy Department of Xiyuan Hospital (CACMS) and have been subjected to aqueous extraction and proprietary processing technology. The daily dosage of LGYY medication is a paste

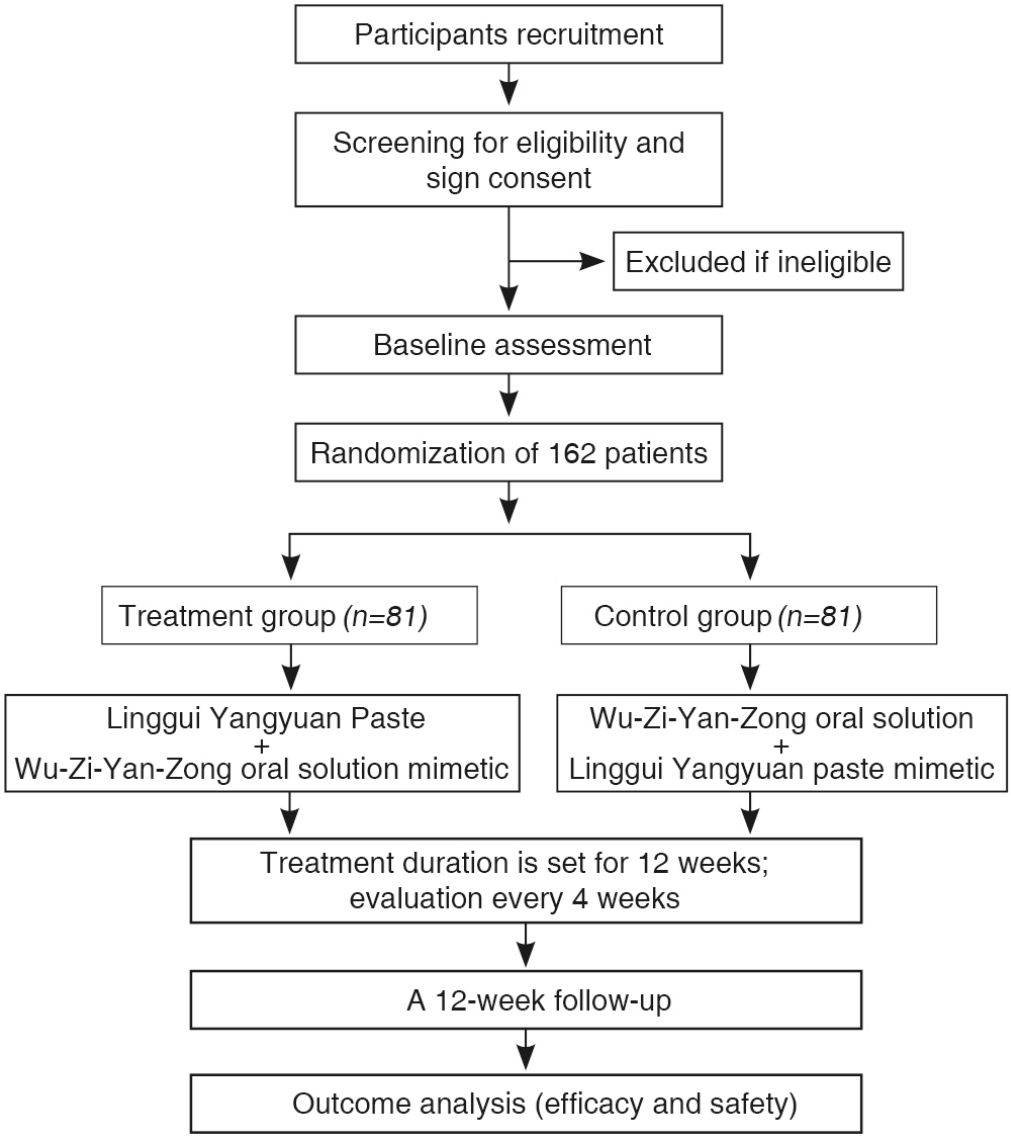

FIGURE 1. Flow chart of the clinical trial (ClinicalTrials.org, NCT05792813).

containing 80 g of raw medicine. Participants in the treatment group will take LGYY or its mimetic in 1 bag twice daily, half an hour after breakfast and dinner. WZYZ (lot: 20220601) will be purchased from Jiangxi Daziran Pharmaceutical Co., Ltd. Ji'an, Jiangxi, China, and the WZYZ mimetic will be prepared by Dong-E-E-Jiao Co., Ltd. Shandong, China. The medication comes in 10 mL bottles of oral liquid. Participants in the control group will take WZYZ or its mimetic, 1 bottle twice daily, half an hour after breakfast and dinner. The intervention period will last 12 weeks [20, 21], during which the participants will be strictly prohibited from adding other drugs or interventions (such as acupuncture) for male infertility to ensure the integrity of the trial and the accuracy of the results.

2.5 Outcome measures

2.5.1 Effective outcome

The primary outcome is the change in TPMSC at week 12 compared to the baseline measurement, and the secondary outcomes will include various semen parameters: semen volume, sperm concentration, total sperm count, PR, PR + NP, Chinese Medicine Symptoms Score (CMSS), spouse pregnancy rate and time to pregnancy [22]. To analyze the data, descriptive statistics will be calculated for the actual values and changes from baseline at each time point. The results observed at all-time points are presented in Table 1.

2.5.2 Safety evaluation

The safety evaluation includes the patients' general conditions, laboratory assessments and incidence of adverse events (AE). The general condition comprises general physical examination status and vital signs, which will be monitored at each visit. Laboratory assessments include routine blood tests, routine urine tests, liver function tests including alanine aminotransferase (ALT) and aminotransferase (AST), kidney function tests including blood urea nitrogen (BUN) and Creatinine (Cr), and electrocardiography, which will be evaluated at baseline and week 12 after treatment. AE will be monitored and recorded throughout the study.

TABLE 1. Study design and treatment schedules.

Time point	Enrollment	Allocation	Post-allocation			Follow-up
	−7–0 d	0 d	4 w ± 3 d	8 w ± 3 d	12 w ± 3 d	24 w
Informed consent	X					
Baseline parameter						
Age	X					
Duration of disease	X					
Disease history	X					
Comorbidity	X					
Concomitant medication	X					
Clinical examination	X					
Enrollment						
Eligibility screen		X				
Informed consent		X				
Allocation		X				
Intervention						
Treatment group		X	X	X	X	
Control group		X	X	X	X	
Effective outcome						
TPMSC	X		X	X	X	
Semen volume	X		X	X	X	
Sperm concentration	X		X	X	X	
Total sperm count	X		X	X	X	
PR sperm rate (%)	X		X	X	X	
PR + NP sperm rate (%)	X		X	X	X	
CMSS	X		X	X	X	
Spouse pregnancy rate (%)	X		X	X	X	X
Time to pregnancy	X		X	X	X	X
Safety evaluation						
General condition	X		X	X	X	
Adverse events			X	X	X	X
Laboratory assessments*	X				X	
Data collection						
Combined medication record	X		X	X	X	X
Medication compliance			X	X	X	
Causes of dropout			X	X	X	X

*"X" indicates yes. TPMSC: total progressive motile sperm count; PR: progressive motility rate; NP: non-progressive motility rate; CMSS: Chinese Medicine Symptoms Score. *: Laboratory assessments include routine blood tests, routine urine tests, liver function tests (ALT and AST), kidney function tests (BUN and Cr) and electrocardiography.*

2.6 Randomization and blinding

Participants will be randomly assigned to two groups using block randomization, and the randomization sequence numbers will be generated by a statistician using the SAS software (version 9.4, SAS Institute, Cary, NC, USA). A stratified block randomization method will be employed, with the study site being used as the stratification factor based on the cause of male infertility (AS or OA). All participants, investigators, data entry staff and statistical analysts will be blinded to the identified information to avoid bias. The LGYY and WZYZ mimetics will be indistinguishable from the actual drugs in terms of shape, size, color, weight, taste, labeling and packing [23]. Personnel unrelated to the trial will handle blinding, randomization and drug dispensing. In case of any AEs or serious AEs, unblinding will be performed, and the blinding code will be broken to ensure the safety and appropriate management of the participants.

2.7 Data monitoring and quality control

To maintain precision and consistency throughout the trial, all investigators will undergo unified training before the study starts, ensuring that all investigators adhere to the standard protocol across different centers. Two trained research assistants will carry out data collection. All investigators and statistical analysts will remain blinded to the treatment allocations until after the completion of statistical calculations. To ensure smooth coordination and monitoring of all aspects of the trial, including recruitment, intervention and follow-up procedures, the principal investigator will oversee and manage these processes. Lastly, a robust data quality control process will be implemented at each participating center to maintain data quality and accuracy.

2.8 Statistical analysis

Data will be presented as mean with standard deviation or percentage and analyzed using the SPSS software (version 25.0, IBM, Chicago, IL, USA). The per-protocol set (PPS) population will be used for analyzing efficacy indicators. For primary efficacy analysis, an analysis of covariance (ANCOVA) will be used, with the change of TPMSC from baseline at 12 weeks of treatment used as the dependent variable, the baseline as covariates, and the group as the fixed factor. For secondary efficacy analysis, multiple time points comparisons between groups will be performed using the repeated-measures mixed-effects linear models. Categorical variables will be analyzed using χ^2 or Fisher's exact test. The time to pregnancy will be compared using Kaplan-Meier. The safety set (SS) will be used for safety evaluation, and descriptive statistics will be used to analyze the safety data. Statistical significance will be determined based on p values < 0.05.

3. Discussion

AS and OA are the primary causes of male infertility, imposing significant psychological and social burdens on patients and their families, often leading to marital challenges and impaired social interactions [9, 24]. However, the exact mechanisms underlying these conditions remain unclear, and current treatments are limited. In Asian countries, TCM has a history of two thousand years in treating male infertility, and over the past decade, TCM treatment for male infertility has gained popularity and recognition due to its effectiveness, convenience, safety and affordability [13]. Although WZYZ is one of the most important and first-line drugs for AS and OA [25–27], many patients may not benefit from this drug. Comparatively, LGYY is a classical Chinese medicinal compound, and our previous clinical research showed that it demonstrated obvious advantages in improving TPMSC, which was also confirmed in animal experiments [16].

Building upon these promising results, we designed this clinical trial to investigate the treatment of AS and OA using LGYY. We hypothesize that LGYY may outperform WZYZ in enhancing TPMSC. The study will be conducted by experts from five tertiary Grade A hospitals in different regions of China, ensuring a robust and comprehensive approach. If the study demonstrates evident advantages of LGYY in treating OA and AS, it could pave the way for a new and effective clinical approach for male infertility (AS and OA), which could significantly benefit patients, clinical decision-makers and policymakers, providing an alternative and more efficient treatment option.

4. Conclusions

This multicenter, double-blind, double-dummy, randomized controlled trial aims to provide valuable insights into the potential efficacy and safety of LGYY compared to WZYZ for male infertility (AS or OA), which could guide clinicians to an alternative drug approach to treat patients with AS or OA.

ABBREVIATIONS

TCM, Traditional Chinese Medicine; AS, asthenozoospermia; OA, oligoasthenozoospermia; LGYY, Linggui Yangyuan paste; WZYZ, Wuzi Yanzong oral solution; TPMSC, total progressive motile sperm count; PR, progressive motility; NP, nonprogressive motility; CMSS, Chinese Medicine Symptoms Score.

AVAILABILITY OF DATA AND MATERIALS

Not applicable as no datasets were generated at this stage, however, the data will be available on reasonable request after the study completion.

AUTHOR CONTRIBUTIONS

SJL—drafted the trial protocol. FW and JG—critically supervised and corrected the manuscript. SJL, QG, CFZ, XJY, ZMH and BY—were referred to and recruited patients. All the authors designed the trial and critically reviewed the manuscript. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Studies involving human participants were reviewed and approved by the Ethics Committee of Xiyuan Hospital, CACMS (Ethical approval no: 2021XLA114-5). The Clinical Trials identifier is NCT05792813. All participants will sign an informed consent form before enrollment.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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