A Randomized, Double-blind, Placebo-controlled Multicenter Clinical Study of Gulingji Capsule in the Treatment of Idiopathic Oligospermia, Asthenia, and Teratozoospermia

2021-01-01

Protocol：

Inclusion Criteria:

Diagnosed as oligoasthenospermia according to the World Health Organization Laboratory Manual for Human Semen Examination and Treatment (5th edition);

initial examination and reexamination of abnormal semen quality shall meet one of the following conditions: sperm density < 15×10^6 / mL or total sperm count < 39×10^6, proportion of forward motile sperm < 32% or total sperm viability < 40%, percentage of normal sperm < 4%;

Exclusion Criteria:

Leucospermia, with testis, epididymitis, prostatitis, severe genital trauma, testicular torsion, urinary tract infection, cryptorchidism, varicocele, and a history of serious medical conditions such as diabetes, tumor history, inguinal and genital surgery.

Testicular volume < 12ml (B-ultrasonic measurement).

BMI < 18.5 or > 32.

Chromosomal karyotype abnormalities.

Patients with endocrine diseases.

Exposure to an occupation or environment with reproductive toxicity.

Drug therapy to improve semen quality has been used in the past 2 weeks.

Hepatobiliary disease, severe renal insufficiency, clinical disease or history of medication known to reduce fertility.

A known or suspected history of allergy to experimental drugs and similar products.

Any circumstance that the investigator considers to be likely to interfere with participation in the study or assessment.

Arms and Interventions Arms

Experimental group: Guilingji capsule Take 2 tablets orally, once before breakfast and dinner, and take them with saline. The total treatment period is 90 days. Drug:

Guilingji Capsule This medicine is capsule medicine, take method is oral.

Placebo Comparator:Control group Placebo Take 2 tablets orally, once before breakfast and dinner, and take them with saline. The total treatment period is 90 days

Drug: Placebo This medicine is capsule medicine.

Visit 1 (before enrollment) :

Medical history and physical examination, chromosome karyotype in peripheral blood.

Testicular volume was measured by external genital examination and color Doppler ultrasonography, and the presence of varicocele was assessed.

Laboratory tests include: Liver and kidney function (alanine aminotransferase, aspartate aminotransferase, creatinine and urea nitrogen), semen analysis (sperm concentration, sperm motile rate, normal sperm rate, sperm DNA fragment index DFI), serum plasma lipids, serum plasma hormone (T, LH, FSH, E2, PRL, SHBG, INH-B, AMH).

Visit 2 (30 days ±3 days) : laboratory examination as above.

Visit 3 (60 ±3 days) : laboratory examination as above.

Visit 4 (90 ±3 days) : laboratory examination as above.

For subjects with large fluctuations in semen routine detection, semen was routinely detected twice a week at each observation point after enrollment, and data were recorded for analysis.

Outcome Measures:

Primary Outcome Measure: 1. Total sperm count in forward motion

Secondary Outcome Measure: 2. Sperm DNA fragmentation rate.

Centers:

All samples were collected from four centers.

Jinling Hospital, Nanjing Jiangning Hospital, Xi 'an Tangdu Hospital and The First Affiliated Hospital of Wenzhou Medical University.

Statistical analysis plan:

SAS 9.2 system was used to program all the statistical processing. The results of measurement data were expressed as mean ± standard deviation. The group T test was

used for comparison of the mean values of the two independent groups, and Satterthwaite was used to correct the T test when there was variance variance between the two groups. The number and percentage of each group were given for continuous variables and the comparison of rates between the two groups was performed by test, or Fisher's exact probability test if necessary. In hypothesis testing, the two-sided test was uniformly used to give test statistics and their corresponding P values. When Fisher's exact probability method was used to directly give P values, $P \leq 0.05$ was considered statistically significant.

Informed consent for clinical studies

Dear subjects:

We invite you to participate in the research project of "Gulingji Capsule for patients with idiopathic oligopathy, asthenia, teratoospermia, randomized, double-blind, placebo-controlled multi-center clinical study". This informed consent provides you with information to help you decide whether to participate in this clinical study. Please read it carefully and speak to the investigator in charge of the study if you have any questions.

This study been reviewed and approved by the Ethics Committee of Nanjing Jinling Hospital.

1. Research background

Infertility is defined as failure to conceive or procreate in a normally fertile couple who have not used contraception for more than 12 months but are having regular life. According to WHO statistics, nearly 80 million couples are infertile (pregnant), accounting for 10% ~ 15% of couples of childbearing age, while male factors account for 30% ~ 40%. With the rapid development of society, accelerated pace of life, environmental pollution and other factors, the incidence of male infertility shows a significant increase trend. Can't find the relevant part of the male infertility patients infertility factor called idiopathic male infertility, the male infertility patients often characterized by abnormal sperm count (including less sperm, no sperm, sperm hidden), or abnormal energy (including weak sperm, dead sperm disease) or sperm deformity, collectively known as idiopathic less weak sperm deformity of idiopathic (OAT).

Reduced fertility is associated with obesity, and abnormal lipid metabolism may be associated with spermatogenesis, maturation and disability, which may lead to male infertility. Our research group previously analyzed the influencing factors of semen parameters in 1231 Chinese infertile men, and found that semen parameters were not significantly correlated with age, obesity indicators such as body mass index, waist circumference, waist-to-hip ratio and waist-to-height ratio and their combination. It was negatively correlated with serum follicle stimulating hormone (FSH) and luteinizing hormone (LH). Another survey of 631 Chinese men with low fertility also showed that semen parameters such as sperm concentration, sperm motility rate (PR+NP), sperm morphology and the total number of normal forward motile sperm were negatively correlated with serum FSH and LH. There was no significant correlation with serum lipid level. However, spermatozoid was negatively correlated with one or more semen parameters: semen volume, sperm concentration, total sperm count, sperm motility rate, forward motility sperm count, and

normal forward motility sperm count (TNPMS). The plasma triglyceride (TG), cholesterol (TC), low density cholesterol (LDL) and high density cholesterol (HDL) of oligozoospermia, asthenospermia and teratozoospermia patients were higher than those with normal relative sperm parameters. These results suggest that abnormal local lipid metabolism in male reproductive system, especially spermatic lipid level, may affect male fertility.

Sperm DNA integrity (DFI) was positively correlated with plasma triglyceride (TG) and total cholesterol (TC) levels in 1010 Chinese men with low fertility, suggesting that abnormal local testicular lipid metabolism was associated with increased sperm DFI. DFI was significantly correlated with all parameters of semen quality, especially TNPMS, and positively correlated with serum and seminal plasma FSH. Sperm DNA integrity is correlated with sperm motility to a certain extent, which is related to male infertility, abortion and birth defects, and is considered to be a new test indicator for evaluating male fertility, especially for idiopathic infertility patients. Sperm DNA fragmentation index (DFI) is of great significance. Therefore, it is concluded that spermatic lipid metabolism disorder may cause increased sperm DNA damage, and the regulation of systemic and local endocrine levels of serum hormone and spermatic hormone may affect the changes of semen parameters, leading to male infertility.

Guilingji is one of China's four secret prescriptions, the beginning of the name "Lao Jun Yishou SAN", the Song Dynasty Taoist Priest Zhang Junfang corrected the secret book, compiled its essence into the cloud Book seven Jian, containing the prescription. In the Ming Dynasty, shao Yuanjie and others added and deleted this recipe and dedicated it to Emperor Jiajing Zhu Houxai. It was named Gulingji and later passed from the palace to the folk and became a Chinese medicine compound refining agent. Formula of rare and precious, set animals (deer antler, hippocampus, sparrow, brain, etc.), plant medicine (ginseng, radix asparagi, eucommia bark, etc.), mineral medicine (large) such as green salt, spirifer 28 flavour, mostly XinWen GanWen product, summarized the main efficacy as solid kidney Yang, both spleen, liver, add fine brain, bones, and for a party, Can play the effect of complementing each other. The medical principle is derived from the Zangdan Classic and huangdi Neijing. The original diseases treated are night dream and excess, waist acid and soft legs, lethargy, memory loss, qi deficiency cough, loss of appetite, cold fear and abdominal pain, five more diarrhea, etc. Comprehensive treatment of the above symptoms, are a series of symptoms of kidney-yang deficiency, widely used in clinical practice.

Previous studies have shown that Guilingji can significantly reduce the serum insulin level of hyperinsulinemia rats, improve the sensitivity of rats to insulin, inhibit lipolysis, and correct lipid metabolism disorders. Long-term application of Guilingji powder in the treatment of hyperlipidemia in middle-aged and elderly men can effectively reduce the total cholesterol (TC), triglyceride (TG) level, improve the level of high density lipoprotein cholesterol (HDL), has a good effect on lowering blood lipid, and can improve appetite, sexual function and sleep. Guiling Ji capsule can also increase the serum testosterone (T) content, T/LH and T/FSH, and significantly improve the sperm density and motility of oligospermia rats. A study of 80 patients with oligasthenospermia treated with Guiling Capsule showed that the semen parameters of the treatment group were significantly improved, and the effect was better than that of the control group. These findings suggest that GuilingJi capsule can improve semen parameters by regulating serum hormone level and systemic/local lipid level.

Combined with the above background, we proposed the following scientific hypothesis: Guiling Ji capsule may regulate systemic/local hormone levels and correct systemic/local lipid

metabolism to improve semen parameters and treat idiopathic oligoasthenia teratospermatosis. To this end, we put forward this topic research, proposed USES the multicenter, randomized, double-blind, controlled, prospective clinical study design, the comparison between the two groups of patients and semen parameters before and after medication, seminal plasma hormone, serum lipid levels and other indicators, in order to make clear turtle guilingji capsule in patients with idiopathic abnormal sperm less weak clinical curative effect. At the same time, serum and seminal plasma samples of the two groups of patients before and after treatment were collected for protein spectrum bioinformatics analysis, and the effective molecules of Gulingji capsule were searched for mechanism research, and finally the effective mechanism of Gulingji capsule in the treatment of idiopathic oligoasthenia teratozoospermia was determined.

2. Research objectives

To investigate the therapeutic effect and mechanism of Guilingji Capsule on idiopathic oligoasthenia teratospermatoses.

3. Requirements for participation in the Institute

1. Inclusion criteria

(1) Diagnosed as oligosthenospermia according to the World Health Organization Laboratory Manual for Human Semen Examination and Processing (5th Edition);

2) Abnormal semen quality during initial examination and reexamination should meet one of the following conditions: sperm density < 15×106 / mL or total sperm number < 39×10^6, proportion of forward moving sperm < 32% or total sperm viability < 40%, percentage of normal sperm < 4%, and total number of moving sperm > 5×10^6;

2. Exclusion criteria

1) Leukocytosis, testicular and epididymitis, prostatitis, severe genital trauma, testicular torsion, urinary tract infection, cryptorchidism, varicocele, and serious medical diseases such as diabetes, history of tumor, history of groin and genital surgery.

2) testicular volume < 12ml (b-ultrasound measurement).

3) BMI < 18.5 or > 32.

4) Chromosomal karyotype abnormalities.

5) Patients with Yin deficiency and fire syndrome (clinical features: dry mouth and dry throat, five upset heat, prone to oral ulcers, slightly red and slightly dry tongue).

6) Patients with endocrine diseases.

7) Exposure to an occupation or environment with reproductive toxicity.

8) Medication to improve semen quality has been used in the last 2 weeks.

9) Hepatobiliary disease, severe renal insufficiency, known clinical disease or medication history that reduces fertility.

10) A known or suspected history of allergy to test drugs or similar products.

11) Any conditions that the investigator considers likely to interfere with participation in the study or evaluation.

4. Research proposal

Study drug names and specifications

Guilingji capsule, produced by Shanxi Guangyuyuan Traditional Chinese Medicine Co., LTD., batch number Z14020687;

Placebo: identical in appearance with experimental drug, produced by Shanxi Guangyuyuan Pharmaceutical Co., LTD.

Treatment options

Before meals, take 2 guilingji capsules orally, once in the morning and once in the evening, and take saline. The total treatment period was 90 days.

5. I need your cooperation to complete the study

Provide true information about your medical history and current medical condition;

Inform the study physician of any discomfort experienced during the study;

Tell the study physician about any new drugs, medications, or herbs you took during the study

Tell the study physician if you have recently participated in other studies or are currently participating in other studies;

Should not take any medication or treatment, including prescription drugs and over-the-counter medicines (including vitamins and herbs), unless approved by the study physician;

Injection of study drugs as directed and visit as required.

Visit 1 (before enrollment) :

Medical history and physical examination, chromosome karyotype in peripheral blood.

Testicular volume was measured by external genital examination and color Doppler ultrasonography, and the presence of varicocele was assessed.

Laboratory tests include: Liver and kidney function (alanine aminotransferase, aspartate aminotransferase, creatinine and urea nitrogen), semen analysis (sperm concentration, sperm motile rate, normal sperm rate, sperm DNA fragment index DFI), serum plasma lipids, serum plasma hormone (T, LH, FSH, E2, PRL, SHBG, INH-B, AMH).

Visit 2 (30 days ±3 days) : laboratory examination as above.

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Visit 4 (90 ±3 days) : laboratory examination as above.

For subjects with large fluctuations in semen routine detection, semen was routinely detected twice a week at each observation point after enrollment, and data were recorded for analysis.

6. Possible side effects, risks and discomfort of participating in the study

If you experience any side effects or discomfort during the study, please report to the study physician immediately. Study doctors will document and even report incidents in detail. If you or your study physician determines that you cannot tolerate these side effects, the study drug may be discontinued completely and you may be withdrawn from the study. If any adverse event occurs during the study, you will receive timely treatment and treatment, and the researcher will evaluate the adverse event. If any adverse event occurs during the study due to the drug or diagnostic examination required by the study protocol and causes harm to you, in addition to receiving active treatment, The investigator will be responsible for the medical expenses and financial compensation required by relevant laws.

Other risks: There may also be risks, discomfort or adverse reactions that are not currently foreseen.

7. Possible benefits of participating in the study

Participation in the study improved semen parameters and increased the chances of pregnancy.

Examination and treatment during the visit were given priority where possible.

8. Privacy

Your medical records will be kept at the hospital, and researchers, research authorities, and ethics committees will be allowed access to your medical records. Your personal identity will not be disclosed in any public report on the results of this study. We will do everything within the law to

protect the privacy of your personal medical information.

Subject's Statement: I have read the above description of this study and am fully aware of the risks and benefits of participating in this study. I volunteered to participate in the study.

I agree □ or refuse □ To use my medical records and pathological examination specimens for research other than this study.

The subjects signature: date:

Participants' contact phone: phone number: