Efficacy and safety of Jie-du-qing-nao granules for first-episode schizophrenics: study protocol for a randomized controlled trial

Ziyan Li
Beijing Anding Hospital https://orcid.org/0000-0002-3770-5309
Yanzhe Ning (yanzhening0923@163.com)
Beijing Anding Hospital
Pei Chen
Beijing Anding Hospital
Yi Zhang
Beijing Anding Hospital
Dongqing Yin
Beijing Anding Hospital
Hong Zhu
Beijing Anding Hospital
Shanshan Liu
Beijing Anding Hospital
Hongxiao Jia
Beijing Anding Hospital

Study protocol

Keywords: Schizophrenia (SCZ), Jie-du-qing-nao granules(JQG), Traditional Chinese medicine (TCM), Randomized controlled trial

Posted Date: August 28th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-22794/v1

Abstract

Background

At present, the focus and difficulty of schizophrenia (SCZ) treatment is to improve cognitive function and negative symptoms. Jie-du-qing-nao granules(JQG) , a traditional Chinese medicine(TCM) prescription , has a good clinical effectiveness in enhancing the cognition and negative symptoms of patients with SCZ. However, its clear effectiveness and safety have not been adequately supported by clinical studies. The main objective of this study is to explore the efficacy and safety of JQG for first-episode schizophrenics.

Methods/design

This trial is a prospective, randomized, single-centered, parallel-controlled clinical study with double-blind design. A total of 96 eligible participants will be randomly assigned to either the study group or the control group in a ratio of 1:1. Participants allocated to the study group will receive JQG and aripiprazole, control group will receive placebo and aripiprazole. The treatment course will last 12 weeks, with follow-up every 4 weeks. Outcome measurements include Positive and Negative Syndrome Scale (PANSS), self face test , MATRICS Consensus Cognitive Battery (MCCB), TNFα, IL-6, IL-1β, BDNF, vital signs, complete blood count, liver and kidney function tests, urinalysis, and electrocardiograph. Adverse reactions will be evaluated using the Treatment Emergent Symptom Scale (TESS).

Discussion

This study will provide evidence for the efficacy and safety of JQG as a complementary approach, which can be initiated following with antipsychotics therapy.

Trial registration

Chinese Clinical Trial Registry, ID: ChiCTR1900028250 . Registered on

December 16, 2019, http://www.chictr.org.cn/edit.aspx?pid=41880&htm=4 .

Background

Schizophrenia (SCZ), a severe mental disorder with high disability, high burden and high risk, affects approximately 1% of the world's population[1]. Drug therapy is currently the main method of treating SCZ. It is confirmed that antipsychotics have a significant effect on improving the positive symptoms of schizophrenia and no determined curative effect in improving negative symptoms[2] and cognitive function[3]. Meanwhile, antipsychotics wil bring numerous adverse effects, such as cardiovascular symptoms, metabolic syndrome, hyperprolactinemia, tardive dyskinesia, extrapyramidal reactions, obesity, constipation and so on[4–7]. It seriously affects both recovery and quality of life. Thus, it is essential to explore other complementary therapies to promote effects for SCZ.

Traditional Chinese medicine(TCM) is an ancient medicine over 2,000 years. Ancient books of TCM have recorded numerous methods of diagnosis and treatment of diseases similar to SCZ. These methods still guide Chinese medicine treatment of SCZ in China today. With the help of modern scientific research methods, limited evidence suggests that TCM combined with antipsychotic can more effectively improve the psychiatric symptoms(like Wendan Decoction[8]), cognitive functions(like Wendan Decoction[8] and Warmsupplementing Kidney Yang Capsule[9]) and lower the side effects of antipsychotics (like Suoquan Pill and Wuling Powder[10]) in patients with SCZ. A systematic review also affirmed the role of TCM as adjuvant therapy in improving psychiatric symptoms and cognitive impairment in patients with SCZ[11]. However, due to the poorly quality of methodologies used in the presently reported studies and relatively limited availability of relevant studies, it is still premature to conclude the overall efficacy and safety of TCM under this context.

Jie-du-qing-nao granules(JQG) is a traditional Chinese medicine prescription created by chinese medical specialist Jia Hongxiao to treat SCZ. It consists of several chinese herbs and mineral drugs: Scutellariae Radix, oriental wormwood, dried rehmannia root, salviae miltiorrhizae, chrysanthemum, thunberg fritillary bulb, Concha Margaritiferallsta, etc. Clinically, JQG has a significant effect in improving the negative symptoms and cognitive level of patients with schizophrenia. However, its clear effectiveness and safety have not been adequately supported by clinical studies.

In this study, we aim to examine the efficacy and safety of JQG as an adjunct treatment for first-episode schizophrenics in 12-week.

Methods/design

Study design

This trial is a prospective, randomized, single-centered, parallel-controlled clinical study with double-blind design. The study design is detailed in Fig. 1.

Recruitment

A total of 96 patients will be recruited from outpatient department of Beijing Anding Hospital affiliated to the Capital Medical University of China. Clinicians will diagnose and screen the patients for eligibility according to the inclusion and exclusion criteria. Potentially eligible patients will be informed and explained the detailed procedures of the study. Only those willing to provide written informed consent will be included to ensure that participation is entirely voluntary. We started recruitment in December 2019 and will finish in December 2020.

Inclusion criteria

- Meet the criteria of schizophrenia in ICD-10
- antipsychotic medication naive patients

- Age ≥16 and ≤ 40 years
- Patient can understand the follow-up questionnaire survey
- Meet the criteria of traditional Chinese medicine syndrome of JQG, which usually manifests as hallucination, delusion, weird thinking, incoherence of thinking, allophasis, infantilism, irritability, dry mouth, constipation, reddened tongue, yellow fur, rapid pulse, stringy pulse or slippery pulse
- Patient or proxy has signed written informed consent

Exclusion criteria

- Have a history of psychoactive substance abuse
- Have severe suicidal tendencies
- Women during pregnancy, lactation or Intending to become pregnant
- With serious heart, liver, kidney, endocrine, blood and other medical conditions
- Intake of antipsychotic medications in the previous 4 weeks
- Unattended
- Participation in other clinical drug trials in prior 30 days
- Compared to baseline, the reduction of PANSS screening score is more than 25%

Randomization, allocation concealment, and blinding

All participants will be randomly allocated to study group or control group (48 cases each) in a 1:1 ratio. An independent administrator manage the random processes. He or she will produce a computer-generated random sequence using SAS software, and seal serially the group assignments in opaque envelopes before the research. Participants will be grouped according to recruitment order and grouping code in the corresponding envelope. All participants, principal researchers, outcome assessors and statistician experts will blind to treatment assignment. In case of adverse events , the blinding should be removed immediately and the reason and time should be recorded in the Case Report Form. The unblinded participant will be excluded from the study.

Interventions

Patients assigned to experimental group will receive JQG and aripiprazole orally after completion of the randomization. And control group will be given placebo and aripiprazole. Aripiprazole is 5mg/tablet and will be provided by Zhejiang Otsuka Pharmaceutical Co, Ltd. JQG and placebo prepared by Beijing Kangrentang Pharmaceutical Co, Ltd, Beijing, China. The placebo is the same in color, smell, taste, appearance, packaging, and tag as JQG, but made from 5% original medicine, dextrin, food colorants, bitters, and water.

Aripiprazole will be started at 2.5mg qd., with an increase of 5mg every 1-2 days to the maximum dose of 20-30mg qd.. JQG or placebo will be brought back by the patient or the patient's caregiver. They will

dissolve granules into 100 ml of boiled water, then take it between 30°C and 36°C. Each time 1 bag of granules, half an hour after meals in the morning and evening. The course of treatment is 12 weeks.

During the trial, trihexyphenidyl 2-4mg/day may be approved for treat aripiprazole - induced extrapyramidal reactions. Zopiclone and zolpidem are allowed to treat insomnia, but cannot be used continuously for more than 1 week. Notably, applying other drugs ,like antipsychotics, sedatives, antidepressants, anxiolytics, mood stabilizers, and other treatment is prohibited.

An overall schedule of trial-related activities are shown in Fig. 2.

Outcome measures

Primary outcome

Positive and Negative Syndrome Scale (PANSS) , a widely recognized rating scale for assessing schizophrenia symptoms[12], will be used as a primary measure of efficacy. We set the decrease of PANSS score before and after treatment as primary outcome. PANSS will be measured by independent professionals at baseline and every 4 weeks during follow-up. We will record the score of each measurement, and compare baseline score with post-treatment score to calculate the reduction rate. The higher reduction indicats greater effectiveness.

Secondary outcomes

- Assessment of cognitive function: comparison of scores of self face test and MATRICS Consensus Cognitive Battery (MCCB) from baseline to every 4 weeks.
- Evaluation of biological indicators: measure TNFα, IL-6, IL-1β and BDNF at before and after 12-week of treatment. We will take 5mL venous blood samples from each participant and store them at a low temperature. Various indexes will be determined by a professional using enzyme-linked immunosorbent assay (ELISA).
- Estimated security: observe variation of vital signs, complete blood count, liver and kidney function tests, urinalysis, and electrocardiograph. Vital signs include blood pressure, heart rate, temperature and weight. Those indexes will be measured at screening time and the end of 12 weeks' follow-up by a researcher using the same testing instruments and methods.

Safety-reporting

In this trial, we will ensure that the study meets the highest ethical standards and patient safety. Treatment Emergent Symptom Scale (TESS) will be used to check the adverse events (AEs) at every visit[13]. Any AEs arising in participants during the intervention will be recorded. Then reporting it to the principal researcher and ethics committee to decide whether the participant needs to be drop out of the trial. In case of serious AEs, the report will be completed by email or telephone within 24 hours.

Data collection

CRFs designed for this study are used for data acquisition. After completion, they will be archived and stored by the principal researchers. Before statistical analysis, paper data will double-entered in Epidata to ensure the accuracy. All original files should be kept for a prescribed time-limit.

Follow-up

After finishing the baseline, participants will begin treatment respectively. Follow-up will be carried out at the 4th, 8th and 12th week after treatment. During this period, all interviews and indicators will be recorded and retained.

Data management and quality assurance

Before this trial, an independent organization will be founded. It is responsible for the data management and monitoring to ensure the accuracy and reliability of the data. Firstly, all investigators were required to abidance by the protocol through onsite training before recruitment. Secondly, any changes to the protocol should be reported to the primary researcher and can only be implemented after recording and permission. Thirdly, members of this organization supervise the collection, entry and storage of data throughout the trial. Researchers will be notified promptly if there are any errors. Fourthly, all electronic and paper data related to this study will be safely kept in the Clinical Research Center of Beijing Anding Hospital.

Sample size

According to previous studies, the response rate of atypical antipsychotics in combination with traditional Chinese medicine in the treatment of schizophrenia was (p1) 95.6%, and atypical antipsychotics for first-episode schizophrenia was (p2)84.3%. Set $\alpha = 0.025$, $\beta = 0.2$, $\Delta=0.3$. Applying superiority test, based on the formula $n1=n2=([(Z(1-\alpha)+Z(1-\beta))]2[p1(1-p1)/k+p2(1-p2)])/[(p1-p2+\Delta)]2$, we used software to calculate the sample size of each group is 40. Meanwhile, considering a 20% dropout rate, we finally decided to collect 48 cases in each group.

Statistical analyses

All data statistics and analysis are conducted by statisticians who using SPSS software (20.0) for Windows (SPSS, Chicago, IL). They will use general descriptive statistics,
repetitive measurement deviation analysis, chi-square or non-parametric test to analyze the data within each group and between groups.

In general statistical description, metrological data are described by mean±standard deviation and enumeration data are represented by constituent ratio. Repetitive measurement deviation analysis will be used to compare metrological data between groups and within groups and chi-square or non-parametric test for enumeration data. The chi-square is appropriate to equal variance and non-parametric test is applicable to unequal variance.

Discussion

At present, there were numerous studies suggesting that the inflammatory activation was associated with schizophrenia. The main inflammatory factors involve TNF-α, IL-6, IL-1β[14]. A meta-analysis showed that TNFα, IL-6 and IL-1β were elevated in patients with schizophrenia[14]. BDNF is a neurotrophic factor that plays an important role in neuronal transport, modulation, and plasticity[15]. Some studies also confirmed that changes of BDNF were accompanied by improvement of cognitive functions, such as memory, spatial direction, and learning[16].

Pharmacological studies of traditional Chinese medicine confirmed that Scutellariae Radix, cape jasmine and honeysuckle main components of JQG, could inhibit inflammatory reaction. On the other hand, another study reported that WSKY, a herbal prescription, was effective in enhancing cognitive performance of schizophrenia via the improving BNDF[9]. In hence, in addition to applying PANSS and MCCB, we attempted to analyze the variation in inflammatory factors and BNDF to help explore the effectiveness of JQG in the treatment of schizophrenia.

However, our study also has several unavoidable limitations. First, as we only focus on patients with first-episode schizophrenia in this study, it is uncertain whether the effects of JQG would be similar in patients with recurrent schizophrenia. Second, as our study will be undertaken in relatively short follow-up period of 12 weeks, it remains unknown whether JQG as an adjunct treatment on first-episode schizophrenia is efficacy and safety over longer periods.

In summary, the aim of our study is to examine efficacy of JQG combined with aripiprazole at 12 weeks on first-episode schizophrenia. This study will provide evidence for JQG as a complementary approach that can be initiated following with antipsychotics therapy.

Abbreviations

SCZ: schizophrenia; JQG:Jie-du-qing-nao granules; TCM:traditional Chinese medicine; PANSS:Positive and Negative Syndrome Scale; MCCB:MATRICS Consensus Cognitive Battery; TESS:Treatment Emergent Symptom Scale; qd.:once a day; CRF:Case Report Form; ELISA:enzyme-linked immunosorbent assay; AEs:adverse events

Declarations

Trial status

The protocol version was 2.0 (October 2019). Recruitment to the study started in December 2019. The trial is currently on going, and recruitment will be completed in December 2020.

Acknowledgements

We appreciate the cooperation and efforts of all the patients and team members who participated in this study.

Funding

The study is supported by Chinese Medicine Science and Technology Development Fund of Beijing (QN 2018 -27), Capital's Funds for Health Improvement and Research (2020-4-2126, 2018-1-2122)Beijing Hospitals Authority's Ascent Plan (DFL20191901), and Talents Training Fund of Beijing (2018000021469G292). These funding and supporting sources have no role in the design of the study and collection, analysis, and interpretation of data or in writing the manuscript.

Availability of data and materials

The authors declare that all relevant data will be included in the article or supplementary files. Additional data are available from the corresponding author on reasonable request.

Authors' contributions

HXJ and YZN conceived the study. YZN is the principal investigator. YZ and SSL helped with the implementation. DQY and HZ conducted primary statistical analysis. ZYL and YZN drafted the manuscript. All authors contributed to the refinement of the study protocol and approved of the final manuscript.

Ethics approval and consent to participate

This study has obtained ethics approval from the research ethics committee of Beijing Anding Hospital, Capital Medical University (ky-2019-77), and will be conducted according to the principles of the Declaration of Helsinki. Trial organization, data management, monitoring and reporting of the study will also be performed in accordance with the guidelines for Good Clinical Practice and other regulations. All participants or their legally authorized representative, included in the current study, gave their informed consent prior to their inclusion in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Rodriguez B, et al. Neuropeptides and oligopeptidases in schizophrenia. Neurosci Biobehav Rev. 2020;108:679–93.

2. Lapish CC, et al. A preclinical assessment of d.l-govadine as a potential antipsychotic and cognitive enhancer. Int J Neuropsychopharmacol. 2012;15(10):1441–55.
3. Matsuda Y, et al. Neural changes following cognitive remediation therapy for schizophrenia. Psychiatry Clin Neurosci. 2019;73(11):676–84.
4. Delgado A, et al. Clozapine in bipolar disorder: A systematic review and meta-analysis. J Psychiatr Res. 2020;125:21–7.
5. Dilks S, et al. Implications of Antipsychotic Use: Antipsychotic-Induced Movement Disorders, with a Focus on Tardive Dyskinesia. Nurs Clin North Am. 2019;54(4):595–608.
6. Marder SR, Cannon TD, Schizophrenia. N Engl J Med. 2019;381(18):1753–61.
7. Gareri P, et al. Use of atypical antipsychotics in the elderly: a clinical review. Clin Interv Aging. 2014;9:1363–73.
8. Deng H, Xu J. Wendan decoction (Traditional Chinese medicine) for schizophrenia. Cochrane Database Syst Rev. 2017;6:CD012217.
9. Guo X, et al. WSKY, a traditional Chinese decoction, rescues cognitive impairment associated with NMDA receptor antagonism by enhancing BDNF/ERK/CREB signaling. Mol Med Rep. 2015;11(4):2927–34.
10. Hung CC, et al. Treatment effects of traditional Chinese medicines Suoquan Pill and Wuling Powder on clozapine-induced hypersalivation in patients with schizophrenia: study protocol of a randomized, placebo-controlled trial. Zhong Xi Yi Jie He Xue Bao. 2011;9(5):495–502.
11. Wei YY, et al. Effectiveness of Traditional Chinese Medicineas as an Adjunct Therapy for Refractory Schizophrenia: A Systematic Review and Meta Analysis. Sci Rep. 2018;8(1):6230.
12. Matsusaki A, Kaneko M, Narukawa M. Meta-analysis of Dropout Rates in Placebo-Controlled Randomized Clinical Trials of Atypical Antipsychotics Assessed by PANSS. Clin Drug Investig. 2019;39(10):917–26.
13. Bellino S, Paradiso E, Bogetto F. Efficacy and tolerability of quetiapine in the treatment of borderline personality disorder: A pilot study. J Clin Psychiatry. 2006;67(7):1042–6.
14. Pedraz-Petrozzi B, et al. Effects of inflammation on the kynurenine pathway in schizophrenia - a systematic review. J Neuroinflammation. 2020;17(1):56.
15. Gokce E, Gunes E, Nalcaci E. Effect of Exercise on Major Depressive Disorder and Schizophrenia: A BDNF Focused Approach. Noro Psikiyatr Ars. 2019;56(4):302–10.
16. Di Carlo P, Punzi G, Ursini G. Brain-derived neurotrophic factor and schizophrenia. Psychiatr Genet. 2019;29(5):200–10.

Figures

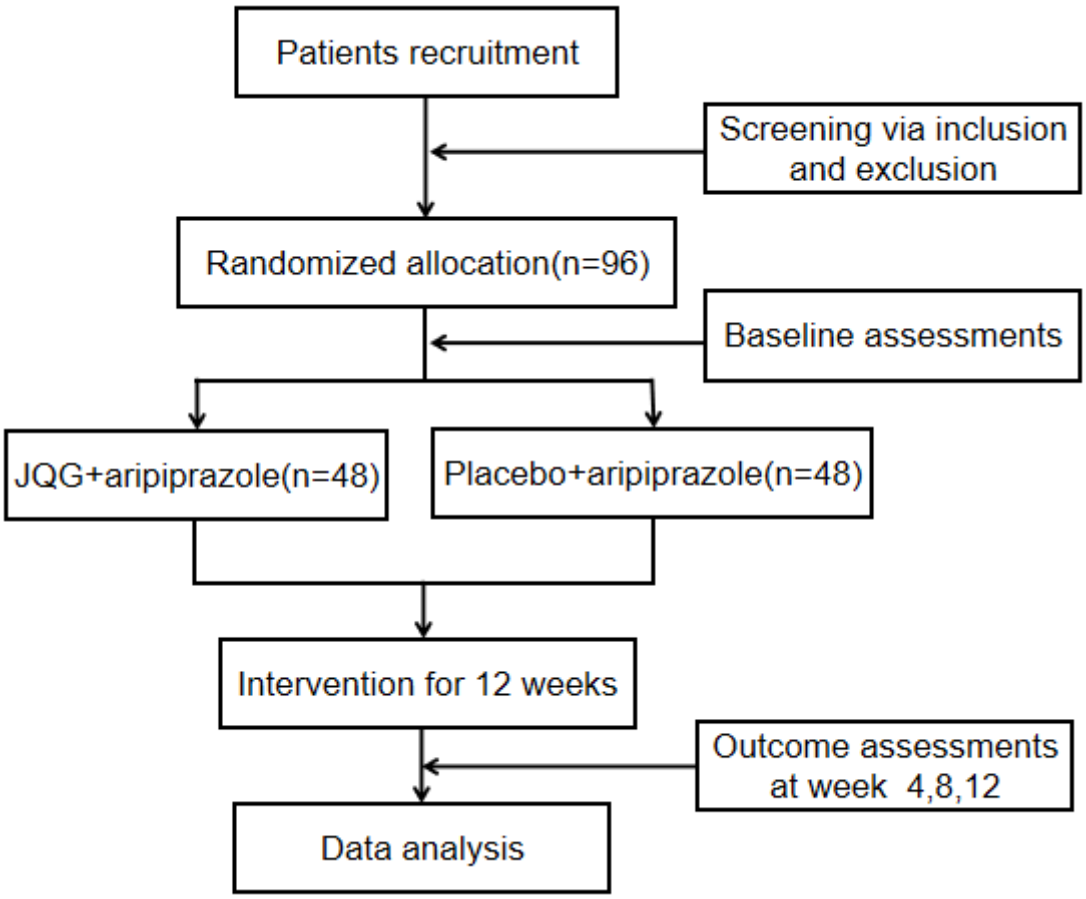

Figure 1

Flowchart of the study design

	Enrolment	Allocation	Post-allocation			
TIMEPOINTS			week0	week4	week8	week12
Eligibility screen	×					
Informed consent	×					
Demographic data	×					
History and symptoms	×					
Allocation		×				
INTERVENTIONS						
experimental group			→	→	→	→
control group			→	→	→	→
ASSESSMENTS						
PANSS			×	×	×	×
Self face test			×	×	×	×
MCCB			×	×	×	×
TNFα			×			×
IL-6			×			×
IL-1β			×			×
BDNF			×			×
vital signs (blood pressure, heart rate, temperature and weight)	×	×				×
complete blood count		×				×
liver and kidney function tests		×				×
urinalysis		×				×
electrocardiograph		×				×
TESS			×	×	×	×

Figure 2

Study schedule

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- renamed3f47d.pdf