Original Article

The effects of combined bromocriptine and Bu-shen-zhu-yun decoction on serum hormones, anxiety, and pregnancy in hyperprolactinemic infertility patients

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Background: Prolactin (PRL) is a protein hormone secreted by the anterior pituitary gland that regulates pituitary hormones. Hyperprolactinemia (HPRL), a pathological phenomenon of excessive PRL, can cause infertility in severe cases and is currently treated mainly with Western drugs, such as bromocriptine, a dopamine agonist (DA). Unfortunately, DAs produce psychological side effects which limit their long-term use. Traditional Chinese medicine (TCM) has minimal side effects and good results spanning many years of research. The combined treatment of TCM and Western medicine may enhance treatment efficacy and improve the long-term prognosis in HPRL. To analyze the effects of Bu-shen-zhu-yun decoction (BSZY-D) combined with bromocriptine on serum hormones, anxiety, and pregnancy in hyperprolactinemic infertile patients.

Methods: One hundred patients diagnosed with HPRL infertility from June 2020 to June 2021 in the gynecology clinic of Jiangsu Provincial Hospital of Traditional Chinese Medicine were selected and grouped by envelope method. After excluding patients who withdrew or missed visits, 37 cases assigned to the control group were treated with bromocriptine, and 40 cases assigned to the observation group were treated with bromocriptine combined with BSZY-D. The patients' PRL and kisspeptin (KP) serum indexes, improvements in infertility, Anxiety Self-Assessment Scale (SAS) scores, and improvements in the Insomnia Severity Index Scale (ISI) scores were compared between the two groups.

Results: At 3 and 6 months of treatment, serum PRL, SAS, and ISI scores were significantly lower, and serum KP was significantly higher in the observation group than in the control group ($P<0.05$). During the study period, the pregnancy rates were 62.50% (25/40) and 37.84% (14/37) in the observation and control groups, respectively. The observation group also had significantly fewer early miscarriages [10.00% (4/40) *vs.* 32.43% (12/37)] and less adverse reactions [7.50% (3/40) *vs.* 24.32% (9/37)] than the control group (all $P<0.05$).

Conclusions: The combination of bromocriptine with BSZY-D was superior to bromocriptine alone in treating HPRL and HPRL-related infertility, which also demonstrated a positive effect on patients' sleep and low mood.

Keywords: Bu-shen-zhu-yun decoction (BSZY-D); bromocriptine; hyperprolactinemia (HPRL); infertility; sleep

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Introduction

Hyperprolactinemia (HPRL), the excess of prolactin (PRL), is a common and challenging disease in gynecology, usually producing reproductive problems in both sexes particularly anovulatory infertility in women. The mechanism of HPRL is complex and is usually considered to be caused by a combination of internal and external factors such as pathology, drugs, and organic heterogeneity. Hence, HPRL can be classified into two subtypes based on etiopathogenesis: organic and functional HPRL. HPRL mainly manifests as elevated serum PRL, negatively affecting patients' reproductive functioning and central nervous system. In mild cases, it may lead to amenorrhea, low menstrual flow, and reduced sexual function, resulting in a lower quality of life. In severe cases, it leads to infertility, which may negatively impact the patient's psychological health and family harmony. The main investigations in the diagnosis of HPRL are hormonal and radiological.

Bromocriptine is one of the first-choice drugs for HPRL, and it has a good control effect on serum PRL and sex hormones (1). However, results from related studies (2) show that bromocriptine can cause serious adverse effects, such as nausea and vomiting, vertigo, and, in severe cases, upright hypotension, cardiac arrest, and vasospasm of the lower limbs. Some patients have also reported hallucinations and delusions. These adverse side-effects of bromocriptine lead to a further decrease in patient compliance and limit long-term treatment (3). In contrast, traditional Chinese medicine (TCM) treatment considers the symptoms and root cause and has reliable efficacy and fewer adverse effects. Thus, the combination of bromocriptine and TCM is feasible. Bu-shen-zhu-yun decoction (BSZY-D) is a common formula used for kidney deficiency-type infertility. It has shown good therapeutic results in various infertility disorders, such as ovulation disorder and polycystic ovary syndrome (4,5). Still, there are very few studies on the combined use of BSZY-D with bromocriptine for infertility treatment. Therefore, we conducted a comparative study of 87 patients to observe the effect of combined bromocriptine and BSZY-D on improving mental status, infertility, and HPRL-related serum indicators of HPRL patients, aiming to provide new options for the treatment of HPRL-infertile patients. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3111).

Methods

General information

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Jiangsu Provincial Hospital of Traditional Chinese Medicine (also named Affiliated Hospital of Nanjing University of Chinese Medicine, No. 2108NL-030-02) and informed consent was taken from all the patients. 100 patients diagnosed with HPRL infertility from June 2020 to June 2021 at the gynecology clinic were selected and grouped by the envelope method. After excluding patients who withdrew, missed visits, or had serious adverse reactions, a total of 37 cases were assigned to the control group, and 40 cases were assigned to the observation group, with the following diagnostic criteria: (I) Western medicine diagnostic criteria: (i) an absence of pregnancy for 12 months without contraceptive sex; (ii) a prolactin (PRL) level >25 μg/L (6). (II) TCM diagnostic criteria: (i) primary or secondary infertility; (ii) syndrome of depression of heart or liver QI; (iii) menstrual disorder with dark red color; (iv) galactorrhea (v) premenstrual abdominal distension and pain; (vi) tinnitus and dizziness; (vii) frequent sighing; (viii) indifferent sexual desire; (ix) breast distension and pain. Additionally, a light tongue color with thin white coating and string or sunken string pulse. The criteria were satisfied if patients met criteria 1a and 1b, two or more criteria from 2c–2i, and the pulse-taking (7).

The inclusion criteria were as follows: (I) individuals aged 20–40 years; (II) patients who met the diagnostic criteria; (III) those who signed the informed consent and cooperated with the study throughout (8).

Patients were excluded if they had any of the following conditions: (I) neurological diseases; (II) organic diseases such as pituitary tumors; (III) other diseases causing infertility, such as premature ovarian failure; (IV) elevated serum PRL due to other causes (exercise, hypoglycemia, etc.) (9).

Medications

Patients in both groups took bromocriptine (Novartis Farma SPA, Italy; approval number: H20160030; specification: 2.5 mg*30 s) after menstruation at a dose of 2.5–3.75 mg/day, gradually increasing to 10–20 mg/day in 2–3 doses, which could only be increased after the diagnosis of the patient's disease by the physician. Patients were advised not to increase or decrease the dose by themselves. In the event of a serious adverse reaction, patients were asked to contact their physician promptly to decide whether to reduce the dosage or suspend the medication.

BSZY-D was added to the observation group's medication regime and consisted of 10 g of deer horn slices (first decoction), 10 g of violet quartz (first decoction), 20 g of dens draconis (first decoction), 12 g of fried white peony root, 18 g of dioscorea rhizoma, 9 g of vinegared radix bupleuri, 10 g of purple salvia miltiorrhiza, 10 g of gambir plant (finally add), 18 g of cuscutae semen, and 12 g of corni fructus, Add 300 mL of water and simmer with 100 mL of water. An amount of 300 mL of water was added, 100 mL was decocted and poured out, and then a further 300 mL of clear water was added and decocted to 100 mL. The decoction was mixed and taken orally twice daily (morning and evening) but suspended during menstruation. The dosage and course of BSZY-D treatment in the present study were based on the previous studies (4,5).

In both groups, the prescribed medication was taken continuously for 3 months, during which time other medications were forbidden. If menstruation did not occur for more than 1 week, patients were advised to have a pregnancy test promptly, and if pregnancy was confirmed, the medication was stopped.

Observed indicators

The following indicators were compared between the two groups of patients:

(I) Baseline information (age, gestation, etc.).

(II) Before treatment, and at 3 and 6 months of treatment, serum PRL and KP indicators were assessed. An amount of 3 mL of venous blood was collected from patients between 9 and 10 am on the 3rd or 4th day of menstruation on an empty stomach and centrifuged after standing at room temperature. Patients were required to sit for 15 min before collection. The serum PRL was detected by electrochemiluminescence immunoassay (Roche Cobase 601), and serum KP was detected by ELISA assay [human kissin (Kp) enzyme-linked immunoassay kit; Jianlai Bio, Shanghai, China].

(III) Anxiety and sleep assessments:
The Anxiety Self-Assessment Scale (SAS) (10) is a 20-item self-report assessment with possible total scores from 20–80. Scores are rated as <50= normal, 50–60= mild, 61–70= moderate, and >70= severe. Individual items within the SAS were compared between the two groups (e.g., "I feel more nervous and anxious than usual", "I feel worried and scared for no reason", "I get upset or panic easily", and "I feel like I might be going crazy").
The Insomnia Severity Index (ISI) (11) is a 7-item assessment of sleep quality and insomnia, where scores between 0–7= nil, 8–14= mild, 15–21= moderate, and 22–28= severe insomnia. Individual items within the ISI were compared between the two groups (e.g., difficulty in falling asleep, difficulty in maintaining sleep, problems with waking up too early, satisfaction with sleep status).

(IV) Pregnancy rate, serum HCG to determine pregnancy, and diagnosis of pregnancy by the intrauterine sighting of the fetal heart.

(V) Adverse reactions, including hematoma of the nostrils, headache and dizziness, nausea and regurgitation, severe constipation, or increased anxiety.

Statistical methods

SPSS v.22.0 software was used to analyze the data. Measurement data are expressed as the mean ± SD ($\bar{x}$±s), and the Student's *t*-test was used to compare the means between groups. Categorical count data are expressed as percentages (%), and the χ^2 test was used to compare between-group differences. A P value <0.05 was considered statistically significant.

Results

Comparison of baseline information between the two patient groups

The results of the comparison showed that there was no significant difference in the baseline information of age, annual income, type of infertility, duration of education, or career between the two groups (P>0.05), allowing a comparative study to be conducted (*Table 1*).

Table 1 Comparison of baseline information between the two patient groups [n, (%)]

Groups	Observation group (n=40)	Control group (n=37)	*t*	P
Careers			0.009	0.995
Regular occupation	17 (42.50)	16 (43.24)		
No regular occupation	14 (35.00)	13 (35.14)		
Unemployed	9 (22.50)	8 (21.62)		
Duration of education (years)			0.035	0.983
≤9	6 (15.00)	5 (13.51)		
9–12	18 (45.00)	17 (45.95)		
12+	16 (40.00)	15 (40.54)		
Age	30.93±5.08	31.08±5.14	0.129	0.900
Annual income			0.076	0.995
≤50,000	11 (27.50)	10 (27.03)		
50–100,000	15 (37.50)	14 (37.84)		
100–200,000	9 (22.50)	9 (24.32)		
≥200,000	5 (12.50)	4 (10.81)		
Type of infertility			0.030	0.862
Primary infertility	17 (42.50)	15 (40.54)		
Secondary infertility	23 (57.50)	22 (59.46)		

Comparison of serum PRL and serum KP between the two patient groups

Before treatment, the comparison of serum PRL and serum KP between the observation and control groups showed no statistically significant difference (P>0.05). At 3 and 6 months of treatment, serum PRL had decreased in both groups but was significantly lower in the observation group than in the control group. Serum KP was elevated in both groups but was significantly higher in the observation group than in the control group (P<0.05) (*Table 2*).

Comparison of SAS and ISI scores between the two patient groups

Before treatment, the comparison of SAS and ISI scores in the observation and control groups showed no statistically significant differences (P>0.05). At 3 and 6 months of treatment, SAS scores and ISI scores had decreased in both groups, but at both time points, the observation group's scores were significantly lower than those of the control group (P<0.05). Of the 20 SAS individual items, 14 items were statistically significant between the two groups at 3 and 6 months (P<0.05), and six items were not statistically significant (P>0.05) ("I have to urinate frequently", "I am suffering from stomach pain and indigestion distress", "my fingers and toes felt numb", "I had bouts of feeling like I was going to faint", "I felt uncomfortable due to bouts of vertigo", "my limbs shook and trembled"). Of the 7 ISI symptoms, except for the two indicators related to difficulty in falling asleep and difficulty in maintaining sleep, all other indicators were statistically different between the two groups after 6 months of treatment (P<0.05) (*Tables 3*,*4*).

Comparison of pregnancy, early miscarriage, and adverse reaction rates between the two groups

During the study period, there were 25 and 14 successful pregnancies, 4 and 12 early miscarriages, and 3 and 9 cases of adverse reactions in the observation and control groups, respectively, with significant differences between the groups (P<0.05) (*Table 5*).

Table 2 Comparison of serum PRL and serum KP between the two groups ($\bar{x}$±s)

Groups	Observation group (n=40)	Control group (n=37)	*t*	P
Serum PRL (ng/mL)				
Before treatment	70.41±15.28	69.37±16.96	0.283	0.778
3 months of treatment	14.27±3.20	18.81±7.03	3.693	*0.001*
6 months of treatment	6.27±1.67	13.36±4.10	10.075	*0.001*
F	594.68	299.20	–	–
P	0.001	0.001	–	–
Serum KP (nmol/L)				
Beforetreatment	10.35±2.13	10.40±2.34	0.098	0.922
3 months of treatment	20.07±1.34	19.12±1.85	2.595	*0.011*
6 months of treatment	21.69±1.42	20.95±1.69	2.086	*0.040*
F	540.67	300.13	–	–
P	0.001	0.001	–	–

Italic P values indicate P<0.05.

Table 3 Comparison of SAS total scores and individual item scores between the two groups ($\bar{x}$±s)

Groups	Observation group (n=40)	Control group (n=37)	*t*	P
SAS (points)				
Before treatment	48.62±5.16	48.76±4.39	0.128	0.899
3 months of treatment	34.10±3.66	42.89±2.80	11.765	*0.001*
6 months of treatment	29.62±2.94	40.51±2.77	16.696	*0.001*
F	243.26	57.54	–	–
P	0.001	0.001	–	–
I feel more nervous and anxious than usual (points)				
Before treatment	2.98±0.58	3.03±0.55	0.387	0.700
3 months of treatment	1.93±0.35	2.95±0.47	10.854	*0.001*
6 months of treatment	1.38±0.49	2.43±0.50	9.303	*0.001*
F	113.45	15.23	–	–
P	0.001	0.001	–	–
I feel afraid for no reason (points)				
Before treatment	2.45±0.60	2.43±0.50	0.158	0.875
3 months of treatment	1.78±0.42	2.38±0.49	5.782	*0.001*
6 months of treatment	1.33±0.47	2.11±0.31	8.523	*0.001*
F	50.33	5.61	–	–
P	0.001	0.005	–	–

Table 3 (*continued*)

Table 3 (*continued*)

Groups	Observation group (n=40)	Control group (n=37)	*t*	P
I get upset or panic easily (points)				
Before treatment	2.75±0.59	2.81±0.70	0.408	0.685
3 months of treatment	1.95±0.71	2.78±0.67	5.265	*0.001*
6 months of treatment	1.68±0.47	2.19±0.40	5.107	*0.001*
F	34.62	12.35	–	–
P	0.001	0.001	–	–
I feel like I might be going crazy (points)				
Before treatment	2.53±0.60	2.59±0.55	0.456	0.650
3 months of treatment	1.93±0.47	2.57±0.50	5.790	*0.001*
6 months of treatment	1.65±0.48	2.24±0.49	5.335	*0.001*
F	29.90	5.41	–	–
P	0.001	0.006	–	–
I feel like everything is going well and no bad luck will happen (points)				
Before treatment	3.43±0.50	3.35±0.48	0.715	0.477
3 months of treatment	2.58±0.55	3.03±0.50	3.747	*0.001*
6 months of treatment	1.85±0.36	2.76±0.49	9.335	*0.001*
F	110.01	13.44	–	–
P	0.001	0.001	–	–
My limbs shake and tremble (points)				
Before treatment	1.58±0.50	1.57±0.55	0.084	0.964
3 months of treatment	1.28±0.45	1.49±0.56	1.820	0.073
6 months of treatment	1.18±0.38	1.41±0.50	2.283	*0.025*
F	8.71	0.82	–	–
P	0.001	0.443	–	–
I'm bothered by headaches, neck pain and back pain (points)				
Before treatment	2.45±0.60	2.43±0.60	0.146	0.884
3 months of treatment	1.95±0.50	2.27±0.61	2.525	*0.014*
6 months of treatment	1.70±0.46	2.19±0.57	4.1654, P=0.0001	*0.001*
F	21.30	1.57	–	–
P	0.001	0.213	–	–
I feel weak and easily fatigued (points)				
Before treatment	3.13±0.52	3.22±0.79	0.595	0.554
3 months of treatment	1.78±0.48	2.73±0.87	5.992	*0.001*
6 months of treatment	1.38±0.49	2.92±0.60	12.375	*0.001*

Table 3 (*continued*)

Table 3 (*continued*)

Groups	Observation group (n=40)	Control group (n=37)	*t*	P
F	136.19	3.89	–	–
P	0.001	0.002	–	–
I feel calm and can sit still easily (points)				
Before treatment	3.50±0.51	3.49±0.51	0.086	0.932
3 months of treatment	1.85±0.36	3.27±0.51	14.199	*0.001*
6 months of treatment	1.75±0.44	2.97±0.44	12.156	*0.001*
F	198.70	10.60	–	–
P	0.001	0.001	–	–
I feel my heart beating fast (minutes)				
Before treatment	2.25±0.49	2.51±0.65	1.991	0.050
3 months of treatment	1.78±0.48	2.35±0.59	4.666	*0.001*
6 months of treatment	1.58±0.50	2.35±0.48	6.882	*0.001*
F	19.70	0.95	–	–
P	0.001	0.391	–	–
I feel uncomfortable due to bouts of vertigo (points)				
Before treatment	1.68±0.47	1.65±0.59	0.248	0.805
3 months of treatment	1.38±0.49	1.65±0.59	2.191	*0.032*
6 months of treatment	1.28±0.45	1.38±0.55	0.876	0.384
F	7.84	2.70	–	–
P	0.001	0.007	–	–
I have bouts of feeling like I am going to faint (points)				
Before treatment	1.73±0.60	1.70±0.57	0.225	0.823
3 months of treatment	1.58±0.55	1.73±0.61	1.135	0.260
6 months of treatment	1.48±0.51	1.54±0.51	0.516	0.608
F	2.06	1.21	–	–
P	0.132	0.302	–	–
I can breathe in and out easily (points)				
Before treatment	3.18±0.55	2.95±0.62	1.725	0.089
3 months of treatment	1.78±0.73	2.81±0.78	5.986	*0.001*
6 months of treatment	1.58±0.50	2.68±0.58	8.933	*0.001*
F	84.02	1.52	–	–
P	0.001	0.223	–	–
My fingers and toes feel numb (points)				
Before treatment	1.43±0.50	1.35±0.54	0.675	0.502

Table 3 (*continued*)

Table 3 (*continued*)

Groups	Observation group (n=40)	Control group (n=37)	*t*	P
3 months of treatment	1.28±0.45	1.35±0.54	0.620	0.537
6 months of treatment	1.23±0.42	1.27±0.45	0.404	0.688
F	2.07	0.30	–	–
P	0.131	0.740	–	–
I am distressed by stomach pain and indigestion (points)				
Before treatment	1.35±0.48	1.38±0.68	0.225	0.823
3 months of treatment	1.28±0.45	1.30±0.57	0.172	0.864
6 months of treatment	1.28±0.45	1.27±0.51	0.091	0.927
F	0.31	0.34	–	–
P	0.735	0.711	–	–
I have to urinate frequently (points)				
Before treatment	1.40±0.50	1.38±0.49	0.177	0.860
3 months of treatment	1.28±0.45	1.38±0.49	0.934	0.354
6 months of treatment	1.28±0.45	1.30±0.46	0.193	0.848
F	0.88	0.34	–	–
P	0.418	0.711	–	–
My hands are always warm and dry (points)				
Before treatment	3.53±0.66	3.57±0.50	0.298	0.767
3 months of treatment	1.83±0.64	3.05±0.66	8.233	*0.001*
6 months of treatment	1.63±0.49	3.32±0.53	14.540	*0.001*
F	120.52	7.77	–	–
P	0.001	0.001	–	–
My face gets hot and blushes (points)				
Before treatment	1.71±0.57	1.68±0.67	0.223	0.824
3 months of treatment	1.33±0.47	1.68±0.67	2.670	*0.009*
6 months of treatment	1.23±0.42	1.49±0.51	2.449	*0.017*
F	10.66	69.45	–	–
P	0.001	0.001	–	–
I fall asleep easily and sleep well at night (points)				
Before treatment	3.45±0.55	3.24±0.43	1.856	0.067
3 months of treatment	1.88±0.52	3.24±0.43	5.249	*0.001*
6 months of treatment	1.73±0.45	3.08±0.28	15.655	*0.001*
F	140.46	2.11	–	–
P	0.001	0.126	–	–

Table 3 (*continued*)

Table 3 (*continued*)

Groups	Observation group (n=40)	Control group (n=37)	*t*	P
I have nightmares (points)				
Before treatment	2.68±0.57	2.43±0.77	1.628	0.108
3 months of treatment	1.83±0.64	2.43±0.77	3.729	*0.001*
6 months of treatment	1.60±0.50	2.30±0.57	5.739	*0.001*
F	39.45	0.41	–	–
P	0.001	0.662	–	–

Italic P values indicate P<0.05.

Table 4 Comparison of ISI total scores and individual item scores between the two groups ($\bar{x}$±s)

Groups	Observation group (n=40)	Control group (n=37)	*t*	P
Total ISI score (points)				
Before treatment	15.43±3.55	15.08±3.12	0.458	0.648
3 months of treatment	12.38±2.86	14.03±3.17	2.401	*0.019*
6 months of treatment	9.88±2.45	13.41±3.28	5.377	*0.001*
F	34.61	2.59	–	–
P	0.001	0.080	–	–
Difficulty in falling asleep (points)				
Before treatment	3.28±0.60	3.16±0.60	0.877	0.383
3 months of treatment	2.05±0.55	2.89±0.57	6.580	*0.001*
6 months of treatment	1.53±0.51	2.70±0.62	9.071	*0.001*
F	105.05	5.55	–	–
P	0.001	0.005	–	–
Difficulty maintaining sleep (points)				
Before treatment	1.98±0.70	2.08±0.55	0.693	0.490
3 months of treatment	1.60±0.59	1.95±0.47	2.864	*0.005*
6 months of treatment	1.23±0.58	1.81±0.46	4.836	*0.001*
F	14.37	2.75	–	–
P	0.001	0.068	–	–
The problem of waking up too early (points)				
Before treatment	2.11±0.72	2.00±0.85	0.614	0.541
3 months of treatment	1.65±0.48	1.86±0.79	1.422	0.159
6 months of treatment	1.55±0.50	1.76±0.72	1.496	0.139
F	10.72	0.86	–	–
P	0.001	0.424	–	–

Table 4 (*continued*)

Table 4 (*continued*)

Groups	Observation group (n=40)	Control group (n=37)	*t*	P
Satisfaction with sleep status (points)				
Before treatment	2.30±0.69	2.32±0.71	0.125	0.901
3 months of treatment	1.90±0.50	2.14±0.75	1.664	0.100
6 months of treatment	1.68±0.47	2.08±0.76	2.801	*0.007*
F	12.52	1.05	–	–
P	0.001	0.352	–	–
Sleep problems hinder your daily functioning (points)				
F	12.76	0.30	–	–
P	0.001	0.740	–	–
How obvious are your sleep problems to others? (points)				
Before treatment	1.55±0.85	1.49±0.51	0.372	0.711
3 months of treatment	1.45±0.75	1.41±0.55	0.265	0.792
6 months of treatment	1.03±0.53	1.35±0.54	2.623	*0.011*
F	5.83	0.64	–	–
P	0.004	0.529	–	–
How worrisome/distressing are your sleep issues? (points)				
Before treatment	2.25±0.78	2.05±0.66	1.210	0.230
3 months of treatment	1.80±0.56	1.92±0.68	0.848	0.399
6 months of treatment	1.40±0.55	1.84±0.69	3.106	*0.003*
F	17.72	0.91	–	–
P	0.001	0.407	–	–

Italic P values indicate P<0.05.

Table 5 Comparison of pregnancy, early miscarriage, and adverse reaction rates between the two groups [n, (%)]

Groups	Number of cases	Pregnancy rate	Early miscarriage rate	Adverse reaction rate
Observation group (n=40)	40	25 (62.50)	4 (10.00)	3 (7.50)
Control group (n=37)	37	14 (37.84)	12 (32.43)	9 (24.32)
χ^2	–	4.677	5.876	4.136
P	–	*0.031*	*0.015*	*0.042*

Italic P values indicate P<0.05.

Discussion

The mechanism of HPRL is a dysfunction of the hypothalamic-pituitary-ovarian axis (HPO), which is affected by several factors, including intracranial tumors, intracranial inflammation, primary hypothyroidism, pharmacological factors, pregnancy, and lactation. This disease has specificity (e.g., organic tissue heterogeneity), which can have a serious impact on the quality of life of patients (12,13). In studies on the treatment of HPRL,

bromocriptine is commonly used as a first-line treatment in Western medicine. For the HPRL patients with micro- and macroprolactinomas, dopamine agonists (DAs) can be applied to normalize of PRL secretion and gonadal function. Currently, the most commonly used DAs are bromocriptine, cabergoline, pergolide and quinagolide. However, these medicines have significant adverse side effects that can affect treatment compliance. Therefore, to enhance patient treatment compliance and improve the limitations on long-term treatment, it is necessary to combine bromocriptine with methods that have fewer adverse effects, milder side effects, and good efficacy. In this paper, we used a combination of TCM BSZY-D and bromocriptine and found that patients who received the combined treatment showed a significant improvement in clinical symptoms, which may be correlated with a more targeted approach and better efficacy when combining TCM and Western medicine treatments.

Related studies (14-16) have concluded that abnormally elevated serum PRL is a sign of HPRL. Serum PRL is typically suppressed by the hypothalamus through dopamine secretion and is stimulated by 5-hydroxytryptamine (5-HT), but under the influence of external factors, dopamine secretion is either suppressed or 5-HT is secreted in large amounts, resulting in an imbalance in the secretion of PRL. High PRL inhibits the pituitary gland's secretion of gonadotropins, leading to abnormal production of estrogen, follicle-stimulating hormone (FSH), and luteinizing hormone, preventing healthy follicle discharge or development. In turn, this can cause irregular menstruation, galactorrhea, and clinical symptoms of infertility. In addition, high prolactin causes negative feedback damage to estrogen, which prevents progesterone synthesis and leads to a thin endometrium, increasing the rate of miscarriage. Western medicine commonly uses bromocriptine as the drug of choice for high serum PRL treatment. Bromocriptine inhibits the secretory activity of prolactin cells by activating the dopamine-like effect, thereby reducing the serum PLR of patients (17). In the present study, serum PRL decreased significantly in both groups of patients. For HPRL with non-neurological diseases and tumor compression, when serum PRL decreases, HPO function is gradually restored, enabling hypothalamic kisspeptin expression to normalize the hypothalamic-pituitary-gonadal (HPG) axis (18,19) Serum KP is a peptide hormone widely distributed in the brain and multiple tissues and regulates cancer cells, reproductive function, and endocrine function. Kisspeptin regulates brain regions associated with individual behavior, and kisspeptin is a possible target of psychosocial stress that inhibits LH (luteinizing hormone) impulses, while the regulation of serum KP can stimulate the secretion of LH and the FSH (20). BSZY-D can increase serum KP expression by affecting widespread prolactin receptors in hypothalamus GT1-7 cells. In turn, this allows regulation of serum hormone (serum LH, FSH, PRL, estrogen, progesterone, etc.) levels and improves ovulation, thus treating infertility and early miscarriage (21,22).

Bromocriptine has significant efficacy in HPRL, but several studies have shown that long-term continuous use of bromocriptine can produce serious adverse effects (23,24). Long-term DA administration can have unwanted psychological side effects, limiting follow-up treatment of patients and negatively affecting their sleep quality. Previous studies provide evidence to support the use of DAs in reducing prolactin levels and persistent HPRL, such as cabergoline (25,26). However, some patients are resistant or intolerant to DAs. Therefore, it is necessary to seek an alternative approach with fewer side effects and more effectiveness. The symptoms of HPRL are highly similar to those of "galactorrhea disease", "infertility", and "amenorrhea" in TCM, which are considered to be symptoms of spleen and kidney deficiency, and liver depression. The patient's inability to have children may lead to depression, resulting in emotional disorders. This can cause patients with Qi and blood disorder, blood does not follow the regular path of xuehai for menstruation, but with liver Qi on the inverse breast for galactorrhea, resulting in high prolactin hyperemia, galactorrhea, menstruation, amenorrhea or infertility. The formula used in the observation group is suitable for those with kidney deficiency-type infertility. In the formula, the primary component is deer horn slices, which have the effect of tonifying the kidney and nourishing Yang. The secondary components are violet quartz, fried white peony root, cuscutae semen, dioscoreae rhizoma, and corni fructus, of which violet quartz calms the heart and tranquilizes the mind, warming both the lung and the uterus. The other four drugs are commonly used to tonify the kidneys, together with radix bupleuri to detoxify the liver and relieve depression, gambir plant to calm the heart and tranquilize the mind, dens draconis to treat palpitations, body heat, and heart trouble, and purple salvia miltiorrhiza to nourish the blood and calm the mind. The whole decoction is well formulated and soothes the heart, liver, and qi. It also nourishes the liver and kidney, strengthens the spleen, and

enriches the blood, meeting HPRL's therapeutic needs (27,28). Several studies have reported the effective effect of TCM on HPRL treatment. A pilot randomized controlled trial on 56 women with idiopathic HPRL showed a role for chamomile in the modulation of prolactin secretion in women by acting on dopamine receptors (29). Besides, the plant species of the Verbenaceae family have been confirmed to play a role in the treatment of gynecological diseases and premenstrual symptoms, such as depression, HPRL and dysmenorrhea (30).

In this study, the overall clinical efficacy in the observation group was superior to that in the control group. Our findings suggested that adding purple fluoritum, gambir plant, and dens draconis in the BSZY-D effectively calmed the mind and resolved insomnia and poor sleep, resulting in significantly lower SAS and ISI scores in the observation group than in the control group. In addition, modern pharmacology has shown that the neutral saponin component of the triple mushroom class in radix bupleuri can regulate the nervous system, and the total glucosides of peonia in white peony can regulate the hypothalamic-pituitary-adrenal axis and enhance immune function, which improves serum PRL and serum KP levels. The sustained decrease in SAS and ISI scores in both groups was also associated with improvement in HPRL. High serum PRL occurs when dopamine secretion decreases, and therefore the administration of bromocriptine produces a dopamine-like effect in patients resulting in improved depressive symptoms and sleep quality (31-33). However, it should be noted that six individual items on the SAS ("I have to urinate frequently", "I am distressed by stomach pain and indigestion", "my fingers and toes feel numb", "I have bouts of feeling like I am going to faint", "I feel uncomfortable due to bouts of vertigo", and "my limbs shake and tremble"), were not statistically significant between the two groups at 3 and 6 months of treatment, which may be related to the fact that specific limbs and urinary organ tissues were less affected and the adverse effects caused by bromocriptine were mild. On the ISI score, at 3 months of treatment, the observation group scored significantly lower than the control group on two items (difficulty in falling asleep and difficulty in maintaining sleep), and at 6 months of treatment, there was a significant difference in six items (the exception being the problem of waking up too early). The analysis suggests that the 6-month results may be related to the alleviation of bromocriptine side effects after the combined application of BSZY-D, while difficulty in falling asleep and maintaining sleep was more serious before treatment and was alleviated more rapidly. While the pregnancy rate was significantly higher in the observation group, the early miscarriage rate was significantly lower than that in the control group due to a greater reduction in serum PRL and more attenuation of estrogenic negative feedback damage. These findings suggest that the lower rate of adverse effects in the observation group may be related to the fact that herbal treatment allowed a reduction in the dosage of bromocriptine (34,35).

The limitations of this study include the small number of patients included in the study and the exclusion of patients with elevated PRL due to pituitary tumors and other organic heterogeneities, which may have led to some bias in the study results. Therefore, more studies with larger sample sizes are needed to verify the efficacy of the combination of bromocriptine with BSZY-D.

In conclusion, bromocriptine combined with BSZY-D has a good therapeutic effect on HPRL and infertility due to HPRL. The combined treatment is superior to bromocriptine alone in improving patients' sleep and emotional symptoms and has potential for future treatment efficacy.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee

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