Postprint: Efficacy and Safety of Risperidone Microspheres for Injection (II) in Patients with Acute-Phase Schizophrenia

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Abstract

Background: Long-acting injectable antipsychotics represent an important treatment option in the full-course management of schizophrenia. Risperidone Microspheres (II) for Injection features an improved formulation that eliminates the need for oral supplementation during treatment and enables rapid onset of action; however, clinical efficacy data for this formulation remain limited.

Objective: To evaluate the efficacy and safety of Risperidone Microspheres (II) for Injection in patients with acute-phase schizophrenia.

Methods: This was a single-arm, multicenter, prospective study conducted at five research centers (Peking University Sixth Hospital, Hebei Mental Health Center, Urumqi Fourth People's Hospital, Taiyuan Psychiatric Hospital, and Tianjin Anding Hospital) between August 2021 and April 2022. Patients aged 18-55 years with acute-phase schizophrenia were enrolled and received flexible-dose treatment with Risperidone Microspheres (II) for Injection at 25 mg/2 weeks, 37.5 mg/2 weeks, or 50 mg/2 weeks, with an 8-week follow-up period. Assessments using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI), and Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale were performed at baseline and weeks 2, 4, 6, and 8. The Personal and Social Performance Scale (PSP) was evaluated at baseline and week 8, and laboratory parameters were collected.

Results: A total of 58 patients were enrolled. At weeks 2, 4, 6, and 8, significant reductions from baseline were observed in PANSS total scores, positive symptom subscale scores, negative symptom subscale scores, general psychopathology subscale scores, and CGI-Severity (CGI-S) scores ($P<0.001$). Response rates based on PANSS total score re-

duction were 37.9% (22/58), 70.7% (41/58), 89.7% (52/58), and 89.7% (52/58) at weeks 2, 4, 6, and 8, respectively. The PSP score at week 8 (71.00$\pm$14.99)$was signi f icantly higher than at baseline$(46.28$\pm$15.43)($P <$ 0.001).$Mean total drug concentrations at weeks 1, 2, 4, 6, and 8 were (12.94$\pm$8.47)\mu g/L$, (13.23$\pm$10.86)$\mu g/L$, (21.09 g/L, respectively. Common adverse events included tremor, dystonia, and constipation, all mild to moderate in severity; no serious adverse events or dropouts due to adverse events occurred. Prolactin levels were elevated at week 8 compared with baseline (P<0.05).

Conclusion: Risperidone Microspheres (II) for Injection can achieve rapid onset of action without oral antipsychotic supplementation, effectively improves multidimensional symptoms in acute-phase schizophrenia, and demonstrates good tolerability.

Full Text

Efficacy and Safety of Risperidone Microspheres for Injection ( ) in the Treatment of Patients with Acute Schizophrenia

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Abstract

Background: Long-acting antipsychotics represent an important therapeutic option in the full-course treatment of schizophrenia. Risperidone microspheres for injection ( ) features an improved formulation that achieves rapid onset without requiring supplemental oral medication during treatment, though clinical studies on its efficacy remain limited.

Objective: To evaluate the efficacy and safety of risperidone microspheres for injection ( ) in patients with acute-phase schizophrenia.

Methods: This single-arm, multicenter, prospective study enrolled patients aged 18–55 years with acute schizophrenia from five centers (Peking University Sixth Hospital, Hebei Provincial Mental Health Center, the Fourth People's Hospital in Urumqi, Taiyuan Psychiatric Hospital, and Tianjin Anding Hospital) between August 2021 and April 2022. Participants received variable doses of risperidone microspheres for injection ( ) at 25 mg/2 weeks, 37.5 mg/2 weeks, or 50 mg/2 weeks, with an 8-week follow-up period. The Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Scale (CGI), and Udvalg for Kliniske Undersøgelser (UKU) Side Effects Rating Scale were administered at baseline and at weeks 2, 4, 6, and 8. Personal and Social Performance (PSP) Scale assessments and laboratory tests were conducted at baseline and week 8.

Results: A total of 58 patients were enrolled. PANSS total scores, positive symptom subscale scores, negative symptom subscale scores, general psychopathology subscale scores, and CGI-Severity (CGI-S) scores decreased significantly from baseline at weeks 2, 4, 6, and 8 (P<0.001). The response rates based on PANSS total score reduction were 37.9% (22/58), 70.7% (41/58), 89.7% (52/58), and 89.7% (52/58) at weeks 2, 4, 6, and 8, respectively. PSP scores at week 8 (71.00$\pm$14.99)$were significantly higher than baseline (46.28\pm15.43) (P < 0.001). Mean plasma drug concentrations reached (12.94\pm8.47)\mu g/L, (13.23\pm10.86)\mu g/L, (21.09\pm13.04)\mu g/L, (2$ g/L at weeks 1, 2, 4, 6, and 8, respectively. Common adverse reactions included tremor, dystonia, and constipation, all mild to moderate in severity; no serious adverse reactions or discontinuations due to adverse events occurred. Prolactin levels increased significantly from baseline at week 8 (P<0.05).

Conclusion: Risperidone microspheres for injection ( ) demonstrates rapid onset without supplemental oral antipsychotics, effectively improves multidimensional symptoms in acute-phase schizophrenia, and exhibits good tolerability.

Keywords: schizophrenia; antipsychotic agents; long-acting antipsychotics; risperidone microspheres for injection ( ); treatment outcome; drug-related side effects and adverse reactions

Introduction

Schizophrenia is a severe and highly disabling psychiatric disorder characterized by complex and diverse clinical manifestations, primarily including positive symptoms, negative symptoms, and cognitive dysfunction [1]. During acute exacerbations, patients may exhibit impulsive and aggressive behaviors [2], posing significant risks to individuals, families, and society [3]. Therefore, rapid and effective treatment during the acute phase is critical for symptom control and relapse prevention [4]. Antipsychotic medications are the first-line treatment for schizophrenia; however, poor medication adherence often leads to recurrent and persistent illness, increasing the burden on patients, families, and society. The "Expert Consensus on Long-Acting Injectable Antipsychotics for

Schizophrenia" (hereinafter referred to as the Expert Consensus) recommends using second-generation long-acting injectable antipsychotics during the acute phase due to the high recurrence rate of schizophrenia [5-6].

Risperidone microspheres for injection was the first second-generation long-acting injectable antipsychotic; compared with oral antipsychotics, it improves patient adherence and reduces rehospitalization risk [7]. However, the early formulation of risperidone microspheres exhibited slow release after injection, requiring concomitant oral risperidone supplementation for the first three weeks, which increased the medication burden on patients. Risperidone microspheres for injection ( ) represents an improved formulation with appropriate modifications. After injection, the drug microspheres release rapidly, quickly increasing the active ingredient's plasma concentration to therapeutic levels, with stable release maintained for 4–5 weeks. By the time of the second injection, plasma drug concentrations approach steady-state levels without requiring supplemental oral medication. Currently, clinical application studies on risperidone microspheres for injection ( ) remain limited. Therefore, this study employed a single-arm, multicenter clinical trial design to evaluate the efficacy and safety of risperidone microspheres for injection ( ) in patients with acute-phase schizophrenia.

Methods

Study Participants

This single-arm, multicenter, prospective clinical trial enrolled patients with acute schizophrenia from five study centers—Peking University Sixth Hospital, Hebei Provincial Mental Health Center, the Fourth People's Hospital in Urumqi, Taiyuan Psychiatric Hospital, and Tianjin Anding Hospital—between August 2021 and April 2022. Inclusion criteria were: (1) diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria [8]; (2) age 18–55 years, regardless of gender; (3) hospitalized patients in the first episode or acute relapse phase, with acute phase defined as PANSS total score $ $70 at screening and baseline, and at least one of delusion, conceptual disorganization, or hallucination items scoring $ $4. Exclusion criteria included: (1) severe or unstable physical illness; (2) comorbid other mental disorders such as intellectual disability, organic brain disorders, or mental disorders due to physical diseases; (3) electroconvulsive therapy within one month before screening; (4) history of psychoactive substance abuse within the past 12 months, significant suicidal ideation, or violent behavior; (5) current or past tardive dyskinesia symptoms or history of neuroleptic malignant syndrome; (6) use of any long-acting injectable antipsychotic within three months before screening or clozapine treatment; (7) previous allergic reaction to any antipsychotic medication.

The study was approved by the Medical Ethics Committee of Peking University Sixth Hospital [Ethics Approval No.: (2021) Review No. (44)]. All patients and their families provided written informed consent.

Treatment Regimen and Concomitant Medications

Patients received risperidone microspheres for injection ( ) (Rui Ke Tuo®, formerly known as Rui Xin Tuo®, Shandong Luye Pharmaceutical Co., Ltd.). Based on clinical judgment, physicians selected variable doses of 25 mg, 37.5 mg, or 50 mg at baseline, week 2, week 4, and week 6, administered once every 2 weeks via alternating intramuscular injection into the gluteal region, for a total of 4 injections. No other antipsychotics were combined during the study period; medications for mood stabilization, sleep improvement, or sedation could continue at fixed doses. Benzodiazepines were permitted for anxiety or emergency use, and anticholinergic drugs could be used for extrapyramidal side effects. For patients who had not previously taken risperidone or paliperidone, oral risperidone tablets were administered once daily at 1 mg for 2 consecutive days to observe for hypersensitivity reactions.

Assessments

Efficacy and Functioning Assessments PANSS ratings were completed at each visit to evaluate efficacy, with subscale scores calculated for positive symptoms, negative symptoms, and general psychopathology. The Clinical Global Impression Scale (CGI) [10] assessed overall illness severity (CGI-S) at each visit and illness improvement (CGI-I) from the second visit onward. The Personal and Social Performance Scale (PSP) [11] evaluated social and occupational functioning at baseline and week 8.

The primary efficacy endpoint was change in PANSS total score from baseline to study endpoint. Secondary efficacy endpoints included changes in PANSS subscale scores at endpoint, PANSS total score reduction rate, PANSS total score response rate, CGI-I improvement rate, and changes in CGI-S and PSP scores. PANSS total score reduction rate was calculated as: (pretreatment total score - post-treatment total score)/(pretreatment total score - 30) × 100%. Response categories were: $ $75% reduction (remission), $ $50% (marked improvement), $ $25% (improvement), and <25% (no response). PANSS total score response rate was defined as the percentage of patients achieving remission, marked improvement, or improvement. CGI-I ratings of 1 (“very much improved”) and 2 (“much improved”) were used to define improvement in this study.

Blood Sample Collection and Drug Concentration Measurement Five milliliters of venous blood were collected at week 1 after the first dose and at weeks 2, 4, 6, and 8 (before injection) to measure total plasma concentrations of risperidone and 9-hydroxyrisperidone using liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Safety Assessments Adverse events were recorded at each visit. The Udvalg for Kliniske Undersøgelser (UKU) Side Effects Rating Scale [12] was used to evaluate adverse reactions at baseline and weeks 2, 4, 6, and 8. Treatment was discontinued for serious adverse reactions or when investigators de-

termined patients could not tolerate adverse effects, with such cases considered dropouts due to adverse events. Prolactin (PRL), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting blood glucose (FBG) were measured, and waist circumference and body weight were recorded to calculate BMI at baseline and week 8.

Visual Analogue Scale (VAS) (0–100 mm) assessments of injection site pain were completed at each visit. Treatment satisfaction was evaluated at week 8 using a 5-point Likert scale (1 = very dissatisfied to 5 = very satisfied), with scores $ $3 indicating satisfaction with the medication.

Statistical Analysis

Data were analyzed using SPSS 25.0 software. Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x}\pm s$), with paired t-tests for before-after comparisons and one-way repeated measures ANOVA for multiple time points, using Bonferroni correction for pairwise comparisons. Non-normally distributed continuous variables were expressed as median (P25, P75), with Wilcoxon signed-rank tests for before-after comparisons; cases with missing values were excluded. Categorical data were expressed as percentages. Statistical significance was defined as $P<0.05$.

The Full Analysis Set (FAS) included all subjects who received at least one dose and had at least one post-baseline assessment. Demographic descriptions and efficacy analyses were performed on the FAS, with last observation carried forward (LOCF) used for patients who did not complete the 8-week treatment. The Safety Set (SS) included all subjects who received at least one treatment and had safety data recorded, with safety assessments performed on the SS.

Results

Patient Disposition and Baseline Characteristics

Of 62 screened cases, 58 were enrolled. Three patients discontinued the study for various reasons, with 55 completing the entire study. The FAS comprised 58 patients, and the SS comprised 58 patients [Figure 1: see original paper]. Enrolled patients had a mean age of $34.6\$\pm10.6 years, with 20 males (34.5\pm4.5 kg/m\hat{}\{2\}. Baseline PANSS score was 92.5\pm16.8, and baseline CGI-S was 5.3\pm\$0.6$.

Dosage Administration

Actual drug injection dosages at each visit are shown in .

Efficacy Outcomes

Significant differences were observed in PANSS total scores, positive symptom subscale scores, negative symptom subscale scores, general psychopathology subscale scores, and CGI-S scores across time points (P<0.001). At weeks 2, 4, 6, and 8, all these scores were significantly lower than baseline (P<0.001) .

PANSS total score reduction rates at weeks 2, 4, 6, and 8 were (20.43$±17.85)±22.22)±26.15)±26.98)±14.99)*we* (t = -11.638, P<0.001).

Plasma Drug Concentrations

Mean total drug concentrations at weeks 1, 2, 4, 6, and 8 were (12.94$±8.47)$\mu g/L$, (13.23±10.86)$\mu g/L$, (21.09±1 g/L, respectively.

Safety Outcomes

No serious adverse reactions occurred, and no patients discontinued due to adverse events. Based on UKU scale results, adverse reactions with >10% incidence possibly related to medication included: tremor (29.3%, 17/58), constipation (27.6%, 16/58), dystonia (25.9%, 15/58), weight gain (24.1%, 14/58), asthenia/fatigue (15.5%, 9/58), somnolence/sedation (15.5%, 9/58), akathisia (13.8%, 8/58), increased sleep duration (13.8%, 8/58), rigidity (12.1%, 7/58), tension/internal restlessness (12.1%, 7/58), difficulty concentrating (10.3%, 6/58), reduced salivation (dry mouth) (10.3%, 6/58), emotional blunting (10.3%, 6/58), and amenorrhea (10.3%, 6/58). All adverse reactions were reported as mild to moderate in severity.

At week 8, patients showed significant increases from baseline in BMI, waist circumference, and PRL levels (P<0.001). No significant differences were observed between baseline and week 8 in TC, TG, HDL-C, LDL-C, or FBG (P>0.05) . Injection site pain was minimal, with median VAS scores of 10 (0, 20) mm. At week 8, 94.3% (50/53) of patients were satisfied with treatment.

Discussion

Acute-phase schizophrenia is characterized by rich and unstable symptoms, with over 20% of patients exhibiting excitement and agitation. Early and rapid control of psychiatric symptoms is crucial for the full-course treatment of schizophrenia [13-14]. Current first-line treatment for acute-phase schizophrenia involves second-generation antipsychotics. Risperidone, the second second-generation antipsychotic introduced after clozapine, has demonstrated well-established efficacy and safety in treating acute-phase schizophrenia over 30 years of clinical use [15-16]. Long-acting injectable antipsychotics offer advantages over oral formulations, including more reliable bioavailability and better patient adherence. Research shows that early initiation of long-acting injectable treatment during the disease course significantly reduces hospitalization rates and treatment

discontinuation [17-18], with shorter intervals between first diagnosis and long-acting injectable use associated with progressively lower hospitalization rates and treatment costs [19]. The Expert Consensus recommends second-generation long-acting injectable antipsychotics as a first-line treatment strategy for the acute phase, particularly those not requiring oral antipsychotic supplementation during initiation [5].

As the first marketed second-generation long-acting injectable antipsychotic, risperidone microspheres has substantial research supporting its efficacy and safety in acute-phase treatment [20-24]. However, the original formulation exhibited delayed drug release, with active drug concentrations often not exceeding 2 g/L after the first injection [25], necessitating concomitant oral supplementation during early treatment. This lag in drug release also increased pharmacokinetic complexity during future medication switches or combinations [26]. Pharmacokinetic monitoring data for the original formulation showed that after three injections of 25 mg, the mean peak concentration of total active ingredients was $(13.0\$\pm2.3)\mu g/L, while three injections of 50 mg yielded (26.5\pm\$11.1)$ g/L [25].

This study measured plasma concentrations after risperidone microspheres for injection ( ) administration, finding total drug concentrations reached $(12.94\$\pm8.47)\mu g/L$ by week 1 after the first dose, indicating rapid drug release. After three variable-dose injections, total drug concentration was $(23.64\pm14.23)\mu g/L$ at week 6, and after the fourth injection, reached g/L at week 8, demonstrating sustained and stable release consistent with its improved pharmacokinetic profile.

Efficacy results showed that by week 2, all PANSS subscale scores had decreased from baseline, with a PANSS total score response rate of 37.9%, indicating rapid improvement in multidimensional psychiatric symptoms and early onset of action. By week 8, the response rate further increased to 89.7%, demonstrating robust acute-phase treatment efficacy. Additionally, CGI-S scores at week 8 were significantly lower than baseline, with CGI-I improvement rates reaching 81.8% by week 8, further supporting these findings. This study suggests that the formulation improvement of risperidone microspheres ( ) maintains the favorable efficacy of the original risperidone microspheres long-acting injection while simplifying administration. BARRIO et al. [27] conducted a case-control study finding that long-acting injectable risperidone demonstrated superior long-term efficacy and social functioning compared to oral antipsychotics in patients with new-onset schizophrenia. KIM et al. [28] found that switching schizophrenia patients from oral antipsychotics to long-acting injectable risperidone improved social functioning at 12 weeks, with benefits maintained through study endpoint. In this study, PSP scores improved significantly after 8 weeks of risperidone microspheres ( ) treatment, consistent with these previous findings.

Regarding safety, observed adverse reactions were primarily extrapyramidal symptoms, including tremor and dystonia, but all were mild to moderate in severity with no discontinuations due to adverse events, indicating good tolerability of risperidone microspheres ( ) for extrapyramidal symptoms. This

aligns with the pharmacological profile of second-generation antipsychotics [29] and is consistent with previous studies on the original risperidone microspheres formulation [30]. Additionally, compared with oral formulations, long-acting injectables exhibit smaller peak-to-trough fluctuations in plasma concentration, higher bioavailability, and sustained, stable drug release, which may contribute to relatively milder adverse reactions. Research has suggested that adverse reactions with long-acting injectable risperidone may be less severe than with oral formulations [31]. However, given the dose-dependent relationship between antipsychotic dose and extrapyramidal symptom risk [32], clinical monitoring and timely intervention are essential, particularly when using higher doses of risperidone microspheres, to minimize risks and optimize adherence.

This study found significantly elevated PRL levels at week 8 compared to baseline. Antipsychotic-induced hyperprolactinemia results from dopamine D2 receptor blockade in the tuberoinfundibular pathway [33], and risperidone is particularly associated with this effect [34]. However, some studies suggest that long-acting injectable risperidone may carry lower risk of PRL elevation than oral formulations, with PRL levels potentially decreasing during treatment [30]. Clinical use of risperidone microspheres ( ) requires monitoring of PRL and related adverse effects, with appropriate management when necessary. This study also found increased BMI and waist circumference at week 8, though other metabolic parameters showed no significant differences from baseline, suggesting low metabolic risk during acute-phase treatment with risperidone microspheres ( ), consistent with short-term studies of the original formulation [35]. Long-term effects on metabolic parameters require further investigation.

VAS scores indicated only mild injection site pain, with no increased pain due to formulation modification. High patient treatment satisfaction further supports the overall favorable efficacy and safety profile of risperidone microspheres ( ).

Study limitations include the lack of a parallel control group, preventing direct comparison of efficacy and safety with other antipsychotics. Additionally, the small sample size necessitates validation in larger clinical trials.

In conclusion, this study demonstrates that risperidone microspheres for injection ( ) achieves rapid onset without concomitant oral risperidone supplementation, significantly improves psychiatric symptoms, accelerates social functional recovery, and exhibits good tolerability. These findings suggest it may offer a new treatment option for early intervention and full-course management of schizophrenia, providing theoretical and empirical support for further clinical research and practice.

Author Contributions: LI Qian was responsible for data analysis and initial manuscript drafting. YAN Baoping, WANG Jian, WANG Yuan, QIN Yingjie, SUN Junwei, DENG Huaili, and QU Xuehui conducted case screening and data management. ZHANG Yunshu, MA Yanjuan, NA Long, REN Zhiyong, and MA Hongjun contributed to project planning and overall execution. SI Tianmei was responsible for overall study design, quality control, and manuscript revision.

Conflict of Interest: None declared.

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Note: Figure translations are in progress. See original paper for figures.