Retrospective analysis of the efficacy and safety of rivaroxaban in the treatment of hepatic sinus obstruction syndrome caused by *Gynura segetum*

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Abstract

Background PA-HSOS is a rare disease and there is no specific treatment for PA-HSOS. Anticoagulant, antithrombotic and microcirculation therapy can alleviate the progression of PA-HSOS. The application of rivaroxaban in patients with PA-HSOS has not yet been reported. The aim of this study was to analyze the efficacy and safety of rivaroxaban in the treatment of pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome caused by *Gynura segetum* (PA-HSOS). Methods A retrospective analysis was conducted with the clinical data of patients with PA-HSOS in the acute/subacute phase caused by taking *Gynura segetum*. The patients were divided into warfarin and rivaroxaban groups according to the anticoagulant therapy they received. Related biochemical indicators were monitored during hospitalization. Liver ultrasound, liver elastography and related biochemical indicators were reviewed every two weeks or one month after discharge. The patients were followed until 1 year after complete remission or death. The efficacy and safety of rivaroxaban was compared with that of warfarin according to the patients' hepatic venous recanalization rates and the occurrence of bleeding events. Results The study included 20 patients, with 10 patients in the warfarin group and 10 patients in the rivaroxaban group. The results showed that the average anticoagulant course in the rivaroxaban group was significantly shorter than that in the warfarin group ($P=0.007$). With treatment, the remission rates of the rivaroxaban group and the warfarin group reached 90%. There was no significant difference in the incidence of adverse reactions or bleeding events between the two groups ($P>0.05$). Conclusions Compared with warfarin, rivaroxaban, a new oral anticoagulant, is convenient and safe for clinical use. It has an obvious effect on PA-HSOS and a low risk of bleeding. It provides a new anticoagulant treatment for PA-HSOS.

Background

Pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome (PA-HSOS) refers to hepatic sinusoidal obstruction syndrome (HSOS) caused by the ingestion of plants containing pyrrolizidine alkaloids (PAs). To date, more than 660 PAs and PA N-oxides have been identified in an estimated 6000 plants^[1]; the most frequent herbal medicine that causes PA-HSOS reported in China is *Gynura segetum*, which is used to relieve pain, improve blood circulation, and dissipate blood stasis^[2,3]. To date, the toxic mechanisms underlying PA-induced toxicity are not fully understood. Research shows that the metabolic activation of PAs is catalyzed by hepatic cytochrome P450 and generates reactive pyrrolic metabolites that bind to cellular proteins to form pyrrole-protein adducts leading to PA-induced hepatotoxicity^[4].

PA-HSOS is a rare disease with a low incidence. At present, there are limited reports about it. The classical triad of PA-HSOS consists of ascites, hepatomegaly, and increased bilirubin levels. The typical manifestations are swelling, damage and shedding of hepatic sinusoid endothelial cells in the hepatic acinus zone III and significant dilation and congestion of the hepatic sinusoids^[5]. The clinical manifestations and test indicators of PA-HSOS are not specific. The diagnosis is mainly based on the history of ingestion of plants containing PAs and imaging examinations. This disease can be confused

with Budd-Chiari syndrome (BCS), decompensated cirrhosis, or acute severe hepatitis, and misdiagnosis prevents prompt treatment. At present, there is no uniform standard for the diagnosis of PA-HSOS. The Baltimore and Seattle standards for hematopoietic stem cell transplantation (HSCT)-induced HSOS (HSCT-HSOS) are often used for reference. The Hepatobiliary Diseases Committee of the Chinese Society of Gastroenterology convened an expert consensus conference on the diagnosis and treatment of PA-HSOS to evaluate current research in China and abroad. The “Nanjing criteria” developed by the committee to diagnose PA-HSOS include a confirmed history of PA-containing plant ingestion and the following: 1) abdominal distention and/or pain in the hepatic region, hepatomegaly and ascites, 2) elevation of serum total bilirubin levels or abnormal laboratory liver tests, and 3) evidence on enhanced CT or MRI, or pathological evidence that rules out other known causes of liver injury^[6]. There is no specific treatment for PA-HSOS, and the mortality rate is high.

PA-HSOS is essentially a liver microcirculatory disorder, so anticoagulant, antithrombotic and microcirculation therapy can alleviate the progression of PA-HSOS. Studies have shown that anticoagulant therapy can significantly improve the cure rate of PA-HSOS patients ($P = 0.004$)^[7]. PA-HSOS patients with ascites and jaundice in the acute/subacute phase should receive anticoagulant therapy as soon as possible. At present, antifibrinogenic therapy is widely used in Western countries, and anticoagulation therapy is less well studied^[8, 9].

Low molecular weight heparin in combination or sequence with warfarin are recommended as anticoagulant regimens in the “Nanjing criteria”^[6]. Previous studies of heparin or low molecular weight heparin in the treatment of a small series of PA-HSOS patients in China reported recovery rates of 70.7%–88.9%^[5]. Low molecular weight heparin is significantly safer than unfractionated heparin. The recommended dose is 100 IU/kg every 12 h, administered via subcutaneous injection and used with caution in patients with renal failure. Warfarin is a vitamin K inhibitor with a definite anticoagulant effect and low cost, but the therapeutic dose range is narrow, individual differences in response are large, and the effectiveness is susceptible to interactions with various foods and medicines. It carries a certain risk of bleeding. During treatment with warfarin, the international normalized ratio (INR) should be detected, and the dosage should be adjusted continuously. It needs to be combined with acid inhibitors. Patient compliance with warfarin therapy is poor.

A new oral anticoagulant (NOAC) rivaroxaban is the first direct oral factor Xa inhibitor. There is no need to monitor coagulation parameters, the anticoagulant effect is exact, and the bleeding risk is low. To some extent, it overcomes the shortcomings of traditional oral anticoagulants and has the characteristics of convenient administration, low bleeding risk, and good patient compliance. Rivaroxaban has been increasingly used as an alternative to warfarin for the prevention of thrombosis in patients with venous thromboembolism (VTE) and atrial fibrillation^[10]. It has been widely used in the treatment of deep venous thrombosis and pulmonary embolism. The preventive dose is 10 mg once a day, and the therapeutic dose is 15 mg twice a day to 20 mg twice a day. Rivaroxaban can also be used in the treatment of portal vein thrombosis (PVT) in patients with and without cirrhosis^[10, 11]. However, in the current research and

guidelines, the anticoagulant treatment of venous thromboembolism of atypical location (VTE-AL), such as the spleen, kidney, mesentery and portal vein, is still dominated by low molecular weight heparin and warfarin.

The main adverse reaction associated with rivaroxaban is bleeding, and attention should be paid to the requirements for liver and kidney function. It is generally believed that the use of rivaroxaban in patients with moderate to severe renal insufficiency needs to be limited. The application of rivaroxaban in patients with PA-HSOS has not yet been reported. This study was a single-center retrospective case-control study designed to evaluate the efficacy and safety of rivaroxaban for the treatment of PA-HSOS.

Ethics, consent and permissions This study was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University. All participants included signed informed consent.

Consent to publish: We have obtained consent to publish from the participant to report individual patient data.

Methods

Subjects

The study included PA-HSOS patients in the acute/subacute phase who visited the Department of Gastroenterology, First Affiliated Hospital of China Medical University from 2017 to 2018. The inclusion criteria were as follows: 1) the diagnosis of PA-HSOS in the acute/subacute phase conformed to the “Nanjing criteria”, 2) age older than 18 years, no genetic relationship with another enrolled patient, and 3) agree to participate in drug research and sign the informed consent. The exclusion criteria were as follows: 1) have a history of alcohol consumption, medication use or other liver diseases such as hepatitis, 2) have a history of other chronic diseases affecting liver function, 3) have contraindications for receiving anticoagulant drugs, and 4) do not consent to participate in drug research.

Data

The following information was collected from the enrolled patients: age, gender, clinical manifestations, history of taking Gynura segetum, disease history, and relevant laboratory indicators and examinations such as alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, gamma-glutamyltransferase (GGT) levels, alkaline phosphatase (ALP) levels, albumin (ALB) levels, total bilirubin (TBIL) levels, direct bilirubin (DBIL) levels, platelet (PLT) counts, prothrombin activity (PTA), D-D levels, liver stiffness, and enhanced CT to detect elasticity and vascular stenosis.

Management

All patients stopped taking Gynura segetum immediately after admission. They were given symptomatic supportive treatment such as liver protection, diuresis therapy, improvement of microcirculation, and intermittent plasma and albumin transfusions. Those with massive ascites underwent intermittent abdominal puncture and ascites drainage. Low molecular weight heparin 4100 iu was injected subcutaneously every 12 h for 2 weeks in all patients. The initial dosage of warfarin was 1.25 mg/day in 10 patients. The INR was monitored 2–3 days later, and the warfarin dosage was adjusted to maintain the INR at 2.0–3.0. Another 10 patients took 10 mg of rivaroxaban orally once a day. Oral anticoagulation was discontinued when there was no intrahepatic vein stenosis and elasticity had recovered on imaging. All patients in the warfarin group took acid inhibitors at the same time to reduce the risk of gastrointestinal bleeding. The rivaroxaban group did not take acid inhibitors.

Follow-up

All patients were reexamined every two weeks or one month by liver ultrasound, liver elastography, routine blood tests, liver function tests, ion levels, coagulation parameters, D-D levels and other indicators. The other therapeutic drugs, such as liver protective treatments, were adjusted according to the improvement of clinical symptoms and biochemical test results. After symptoms disappeared and liver function returned to normal, liver protection therapy was discontinued. The length of the course of anticoagulation was decided according to whether there were vascular stenosis and elasticity on imaging. Rivaroxaban was stopped after patients had normal elasticity and hepatic vascular patency. Follow-up continued for 1 year after the condition was completely relieved or the patient died. Safety was assessed based on the occurrence of bleeding events in patients, including CRNMB, major bleeding, and major bleeding and CRNMB.

Statistical analysis

Normally distributed continuous variables are represented as the means $\pm$ standard deviation; otherwise, the data are described as the medians (interquartile ranges). Count data are expressed as numbers and percentages. Independent t tests were used for comparisons of continuous data, and the Mann-Whitney U test was used for data with a skewed distribution. The Chi-square test or Fisher's exact test was used for comparisons of count data. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with IBM SPSS 20.0.

Results

Patient characteristics

The study included 28 patients and excluded 4 patients with a previous history of alcohol consumption, 2 patients without follow-up data, and 2 patients with incomplete data; eventually, 20 patients were

enrolled, with 10 patients in the warfarin group and 10 patients in the rivaroxaban group. All patients ranged from 43 to 77 years old, with 7 males and 13 females. The patients were mainly taking Gynura segetum due to low back pain, general health care, and other reasons. The daily dose was approximately 5 g~30 g, and the continuous duration during which it had been taken was 2 weeks to 2 years. There were 2 patients with hypertension and 2 patients with diabetes mellitus in both groups; furthermore, there was 1 patient with a hepatic hemangioma in the rivaroxaban group, and 1 patients with a hepatic cyst in the warfarin group. In both groups, the hepatic parenchyma showed characteristic “map-like” and “patchy” nonuniform enhancement in the venous phase, and in the balanced phase, the hepatic veins became thinner, the blood flow velocity slowed down and the elasticity increased significantly. All patients had ascites, and 2 patients each in the warfarin and rivaroxaban groups had umbilical vein opening. There were 2 patients with PVT in each group; 2 patients in the warfarin group and 1 patient in the rivaroxaban group had splenomegaly, while 1 patient in each group showed a decrease in liver volume and a disordered proportion of each lobe. The general characteristics of the study subjects are shown in Table 1, and the comparison of the clinical data is shown in Table 2. There were no significant differences in age, sex, duration of taking Gynura segetum, biochemical indicators, or elasticity between the two groups ($P>0.05$).

Outcome and prognosis

One patient in the warfarin group did not regularly undergo reexaminations of the INR after being discharged from the hospital. After taking the medicine for 40 days, a massive hemorrhage of the digestive tract and urinary tract occurred, which improved after stopping the medicine. The remaining patients underwent regular reexaminations of their INRs. Four patients had CRNMB, which manifested as gingival bleeding, epistaxis, and skin ecchymosis; this improved after dose reduction, and no other serious adverse reactions occurred. Six patients in the rivaroxaban group had limb itching and needle-like pain approximately one week after initiating treatment. The patients were asked to take the medicine orally every other day, and all of the symptoms were relieved. Three patients presented with CRNMB, which manifested as gingival bleeding, epistaxis and skin ecchymosis; all symptoms improved after dose reduction, and no severe adverse reactions occurred. One patient in each group developed hepatic failure and hepatic encephalopathy during treatment and died after leaving the hospital. The remaining patients were discharged after clinical remission and cured after regular reexamination and therapy. No patients underwent interventional therapy. The recanalization rate of hepatic vessels, the incidence of hemorrhage and mortality during treatment are compared in Table 3. There was no difference in the anticoagulant effect between the rivaroxaban group and warfarin group, but the treatment course of the rivaroxaban group was shorter, no additional acid inhibitor was needed, and the patients' compliance was better.

Discussion

In this study, we can see that rivaroxaban is effective for the treatment of PA-HSOS. The majority of patients with PA-HSOS experienced relief of their symptoms after approximately one month. Ultrasound

showed blood flow in the three hepatic veins, and the blood test indexes returned to normal or nearly normal. During anticoagulation, vaginal bleeding, bloody ascites and other bleeding tendencies appeared in some patients, all of which improved after dose reduction, and no serious adverse events occurred due to bleeding. There was no significant difference in the incidence of bleeding events between the rivaroxaban group and warfarin group, which may be related to the small sample size. The duration of anticoagulation therapy in the warfarin group was longer than that in the rivaroxaban group, and the difference was statistically significant.

A study^[12] in 2015 assessed for the first time the difference in the risk of bleeding between traditional anticoagulants and direct oral anticoagulants (DOACs) in patients with liver cirrhosis. Thirty-nine patients with liver cirrhosis with CTP grades A and B were enrolled in the study. They were divided into the traditional anticoagulation (warfarin and low molecular weight heparin) group and the DOAC (factor Xa inhibitors: apixaban and rivaroxaban) group. The results showed that there was no significant difference in the risk of bleeding between the two groups ($P = 0.9$). Similar conclusions were drawn from a subsequent study^[13]. Animal studies showed that rivaroxaban could help to alleviate hepatocyte fibrosis and reduce portal pressure in mice^[14–16], which provided support for the application of rivaroxaban in patients with liver cirrhosis.

In recent years, research on rivaroxaban for the treatment of VTE-AL has gradually increased. A study showed that the VTE recurrence and bleeding rates for NOACs used for VTE-AL are not different from those in patients with VTE-TL and are similar to those for enoxaparin^[17]. Studies on PVT show that rivaroxaban is effective in the treatment of PVT with a low risk of bleeding and is superior to traditional oral drugs^[11, 18, 19]. At present, there are few studies on the application of rivaroxaban in patients with liver cirrhosis and liver dysfunction. It is generally believed that patients with liver diseases at risk of coagulation abnormalities and clinical-related bleeding, including patients with liver cirrhosis CTP grade B and C, should not use rivaroxaban.

To date, the application of rivaroxaban for the treatment of PA-HSOS has not been reported. Referring to the application of rivaroxaban in PVT and other abdominal organ venous embolism diseases, this study innovatively applied low molecular weight heparin in sequence with rivaroxaban oral treatment of PA-HSOS. Considering the abnormal liver function and coagulation function of these patients, they were given a preventive dosage of 10 mg once a day. The results showed that there was no difference in the anticoagulant effect between the rivaroxaban group and warfarin group, but the treatment course of the rivaroxaban group was shorter, no additional acid inhibitor was needed, and the patients' compliance was better.

In summary, the main reasons PA-HSOS patients take Gynura segetum are general health care and the treatment of lumbago and leg pain. Most patients experienced an onset of the adverse reaction within one month after taking Gynura segetum. More patients were females than male. Laboratory examinations of PA-HSOS are not specific. Imaging examinations play an important role in the diagnosis of PA-HSOS^[20–22]. At present, there is no effective treatment for PA-HSOS. Early detection and active

treatment can greatly reduce the mortality rate of patients. The clinical manifestations and examinations of the patients included in this study were typical, with a clear diagnosis and representative results.

A limitation of this study is that it was a single-center study, with few patients and no randomization or blinding. The number of included patients was small, and there is a lack of long-term follow-up data on treatment effects; therefore, further large-sample studies are needed. The replacement of warfarin anticoagulant therapy with rivaroxaban for PA-HSOS has greatly improved the safety of treatment and provided new methods for the diagnosis and treatment of the disease. The application of anticoagulant therapy in patients with PA-HSOS is still being explored. The clinical application of rivaroxaban anticoagulant therapy in patients with PA-HSOS, especially in patients with decompensated CTP grade C cirrhosis, still needs caution.

Declarations

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Author contributions

HB and DL are the first authors, BC and YL are corresponding authors. BC and YL carried out clinical studies; XH, JT, YW, RA and NW carried out data collection; HB and DL carried out data analysis and manuscript writing.

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Availability of data and materials

The datasets supporting the conclusions of the current study are available at First Affiliated Hospital of China Medical University, which are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of Ethics Committee of the First Affiliated Hospital of China Medical University, and written informed consents were obtained from all enrolled patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Comparison of the general characteristics of the two groups

	Warfarin group (N=10)	Rivaroxaban group (N=10)	<i>P</i>
Source of <i>Gynura segetum</i>			
Self-planted	6	7	0.648
Bought at a pharmacy or online	4	3	0.648
Method of consuming <i>Gynura segetum</i>			
Grind into powder and flush	2	2	1
Boil in water	4	5	0.661
Soak in water	3	2	0.615
Soak in wine	1	1	1
First symptoms			
Abdominal distention	2	2	1
Abdominal distension, fatigue, poor acceptance	5	4	0.661
Abdominal distension, abdominal pain	2	3	0.615
Fatigue, emaciation	1	1	1
Positive signs on physical examination			
Abdominal bulging and mobile voiced sound	10	10	1
Upper abdominal tenderness	2	3	0.615
Edema of lower limbs	2	2	1
Jaundice	3	2	0.615
Subcostal palpable spleen	1	1	1
Ascites level			
Light	2	1	0.542
Moderate	6	7	0.648
Severe	2	2	1
Anamnesis			
Hypertension	2	2	1
Diabetes	2	2	1
Hepatic hemangioma or cyst	1	1	1

Table 2 Comparison of clinical data between the two groups

Item	Warfarin group (N=10)	Rivaroxaban group (N=10)	Statistic	<i>P</i>
Age	60.50±10.26	60.20±11.03	t=0.063	0.95
Male/female	4/6	3/7	χ ² =0	1
Duration of taking Gynura segetum (months)	3.25 [0.88, 12.00]	1.25 [0.50, 7.50]	U=44	0.684
ALT (U/L)	93.00 [24.50, 244.25]	45.00 [19.25, 174.75]	U=39	0.436
AST (U/L)	190.50 [57.50, 270.25]	61.50 [49.00, 239.00]	U=36.5	0.315
ALP (U/L)	154.50 [67.25, 202.25]	140.00 [109.00, 228.25]	U=62	0.393
GGT (U/L)	215.00 [109.25, 342.75]	113.00 [69.75, 356.25]	U=44	0.684
TBIL (μmol/L)	47.70 [29.30, 61.63]	33.95 [21.75, 43.28]	U=32	0.19
DBIL (μmol/L)	22.55 [7.55, 32.05]	19.65 [12.63, 26.60]	U=49	0.971
ALB (g/L)	27.20 [24.68, 30.28]	27.95 [26.30, 30.98]	U=59.5	0.481
PT (s)	16.70 [15.05, 19.18]	18.05 [15.73, 19.13]	U=55	0.739
Fg (g/L)	1.88 [1.64, 2.92]	2.74 [1.69, 3.81]	U=63.5	0.315
PTA (%)	60.20±14.58	60.30±13.53	t=0.015	0.988
INR	1.49±0.26	1.44±0.20	t=0.427	0.674
D-D (μg/mL)	3.10±1.65	3.07±1.94	t=0.038	0.970
PLT (10~9/L)	105.50 [81.00, 211.00]	123.50 [111.00, 158.25]	U=63	0.353
Hepatic elasticity (kPa)	41.85 [34.10, 53.33]	38.15 [26.70, 55.93]	U=46	0.796
Anticoagulation course (days)	90.00 [90.00, 90.00]	30.00 [30.00, 90.00]	U=15	0.007
Hospitalization time (days)	22.00 [14.75, 24.00]	18.50 [14.00, 25.25]	U=46	0.796

Table 3 Comparison of hepatic vascular recanalization rates, hemorrhagic events and mortality rates between the two groups

	Warfarin group (N=10)	Rivaroxaban group (N=10)	<i>P</i>
1-month recanalization rate	40%	60%	0.39
2-month recanalization rate	60%	70%	0.65
3-month recanalization rate	90%	90%	1
Incidence of all bleeding events	5	3	0.37
Incidence of massive hemorrhage	10%	0%	0.32
Incidence of CRNMB	40%	30%	0.65
Incidence of massive hemorrhage with CRNMB	0%	0%	1
Fatality rate	10%	10%	1