

Cardiovascular Reviews

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Cardiovascular Reviews

Focus and Scope

Cardiovascular Reviews publishes peer-reviewed research articles across basic, translational, and clinical cardiovascular medicine. The journal aims to enhance insight into cardiovascular disease mechanisms and the prospects for innovation. The Journal covers all topics within cardiology and cardiovascular biology with an emphasis on studies that challenge the status quo of treatments, at the molecular, sub-cellular, cellular, organ, and organism level, and of clinical proof-of-concept and translational studies and practices in cardiovascular care or facilitate the translation of scientific advances into the clinic as new therapies or diagnostic tools. Manuscripts are expected to provide a significant contribution to the field with relevance for cardiovascular biology and diseases.

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Study on the Effect of Percutaneous Coronary Intervention in the Treatment of Chronic Coronary Syndrome

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Abstract: Objective: To analyze the clinical effect of percutaneous coronary intervention in the treatment of chronic coronary syndrome. Methods: 120 cases of chronic coronary syndrome patients who received inpatient treatment in a hospital from July 2023 to June 2024 were selected as the object, and were divided into the control group and the observation group using the mean score method, each with 60 cases, the control group was treated with conventional medications (aspirin, carbamazepine, β -receptor blockers, angiotensin-converting enzyme inhibitors, statin and other medications), and the observation group was treated with percutaneous The observation group implemented percutaneous coronary intervention based on this treatment, comparing the therapeutic effects of the two groups. Results: The treatment efficiency of the observation group (98.33%) was significantly higher than that of the control group (86.67%), and the difference was statistically significant ($P < 0.05$); before treatment, the IVPWTd and LVEDd indexes of the patients in the control group and the observation group were (10.39 ± 0.86) mm, (55.36 ± 5.67) mm and (10.41 ± 0.78) mm, (56.01 ± 6.80) mm, respectively. The difference was not statistically significant ($P > 0.05$); after 3 weeks of treatment, all the indexes of the two groups decreased significantly, respectively (9.76 ± 0.62) mm, (53.28 ± 5.63) mm and (8.56 ± 0.49) mm, (49.65 ± 5.47) mm, and the observation group was significantly lower than the control group, and the difference was statistically significant ($P < 0.05$). In the control group, 3 cases of arrhythmia and 2 cases of coronary artery spasm occurred during the treatment period, and 1 case each of residual cardiac insufficiency, acute thrombosis, chronic renal impairment, and cardiogenic death, with a total incidence rate of 15%, while in the observation group, only 1 case of arrhythmia and 1 case of coronary artery spasm occurred, with a total incidence rate of 3.33%, and the difference between the groups was statistically significant ($P < 0.05$). Conclusion: Percutaneous coronary intervention for the treatment of chronic coronary syndrome combined with renal disease is effective, can significantly improve the level of patients' left ventricular function and reduces the risk of related complications, and is recommended to be popularized and applied in the clinic.

Keywords: Chronic Coronary Syndrome; Percutaneous coronary intervention; Pharmacological treatment; Left ventricular function; Complications

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1. Introduction

Chronic Coronary Syndrome (CCS) is a clinical syndrome caused by insufficient blood supply to the myocardium due to coronary atherosclerosis, with chest pain as the main manifestation. Its main pathophysiological mechanisms include the formation of coronary atheromatous plaques, stenosis of coronary arteries, and abnormal endothelial function of the vasculature, which ultimately leads to myocardial ischemia ^[1]. With the aging of the population and lifestyle changes, the incidence of CCS has been increasing year by year and has become one of the major diseases that threaten public health worldwide ^[2]. Conventional treatment options for CCS include antiplatelet agents, beta-blockers, statins, and angiotensin-converting enzyme inhibitors (ACEIs), etc., which are effective in relieving symptoms, stabilizing plaques, and improving the prognosis, but they are not effective in some cases with persistent symptoms or more advanced lesions. However, in some patients with persistent symptoms or complex lesions, purely pharmacological treatment cannot adequately alleviate myocardial ischaemia, and may even lead to a series of complications such as cardiac insufficiency, arrhythmia, coronary artery spasm, acute thrombosis, chronic renal impairment, cardiac death, etc. For this reason, it is necessary to seek a safer and more efficient means of treatment ^[3]. Percutaneous Coronary Intervention (PCI) is a minimally invasive surgical technique in which a balloon or stent is introduced into narrowed coronary arteries through a catheter to dilate the blood vessels to restore normal blood supply to the myocardium, and has achieved remarkable results in improving patients' symptoms, decreasing cardiovascular events, and improving survival rates since its introduction in the 1980s. Since its introduction in the 1980s, it has achieved remarkable results in improving patients' symptoms, reducing cardiovascular events, and improving survival, especially with the advancement of technology, improved equipment, and the use of pharmacological stents, it has become the standard reperfusion therapy. However, the effectiveness of PCI and its comparison with pharmacological treatment in patients with chronic coronary syndromes remains controversial ^[4]. For this reason, the present study was conducted to investigate the role of PCI in the treatment of chronic coronary syndromes in a small-sample clinical trial, to analyze its effect on symptom improvement, cardiovascular events and survival, and to assess the occurrence of complications, to provide a reference for clinical practice.

2. Information and methodology

2.1. General information

120 patients with chronic coronary syndrome who received inpatient treatment in a hospital from July 2023 to June 2024 were selected and divided into a control group and an observation group of 60 cases each using the mean score method. In the control group, there were 42 males and 18 females; the age range was 43–78 years old, with a mean age of (52.5 ± 9.3) years old; disease type: 22 cases of acute myocardial infarction and 38 cases of unstable angina pectoris. Treatment was given (aspirin, carbamazepine, β -blockers, angiotensin-converting enzyme inhibitors, statins and other drugs). In the observation group, there were 40 males and 20 females; the age range was 42–77 years old, with a mean age of (51.9 ± 10.1) years old; disease type: 25 cases of acute myocardial infarction and 35 cases of unstable angina. Percutaneous coronary intervention (PCI) was implemented. The difference between the general clinical data of the two groups of patients was not statistically significant ($P > 0.05$) and was comparable.

Inclusion criteria: (1) Chronic Coronary Syndrome (CCS) was clearly diagnosed according to the diagnostic criteria of “Chronic Coronary Syndrome Diagnostic and Treatment Guidelines” ^[5]. (2) The age range is 42–78 years old, and the gender is not limited. (3) Indications for PCI treatment were met, and the patients and their families signed an informed consent form and agreed to receive treatment and follow-up.

Exclusion criteria: (1) Patients with pre-existing severe cardiac insufficiency or left ventricular ejection

fraction (LVEF) < 30%, who cannot tolerate PCI surgery. (2) There are clear bleeding disorders or coagulation disorders, which are not suitable for long-term antiplatelet or anticoagulation therapy. (3) Those with combined severe hepatic and renal insufficiency, active peptic ulcer or malignant tumor. (4) Those with a previous history of cardiac bypass surgery or coronary artery structural abnormality, are unsuitable for PCI intervention.

2.2. Methodology

2.2.1. Control group

Conventional drug treatment was given. On the first day of hospitalization, patients were given 300 mg of aspirin (Bayer Healthcare Ltd.; J20130078; 100 mg/tablet × 30 tablets/box) chewable treatment with Carbamazepine (AstraZenecaAB; J20171077; 90 mg/tablet × 14 tablets/box; 180 mg) oral treatment. Starting from the second day, oral aspirin (100 mg, 2 times) and carbamazepine (90 mg each time, twice daily) were continued. In the absence of contraindications, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and statins were administered as early as possible, including:

- (1) Metoprolol (AstraZeneca Pharmaceuticals Co., Ltd; H20090467; 47.5 mg/tablet × 14 tablets/box; after meals, starting dose of 25–50mg, 1–2 times a day, adjusted according to the patient's blood pressure and heart rate after 7 days).
- (2) Enalapril (Hangzhou Merck Sharp & Dohme Pharmaceutical Co., Ltd; H10950028; 10 mg/tablet × 14 tablets/box; initial dose of 5 mg once a day, can be adjusted to a maximum of 20 mg/day, divided into 1–2 times according to the blood pressure).
- (3) Atorvastatin (Pfizer Pharmaceutical Co. Ltd; H20140091; 20 mg/tablet × 7 tablets/box; starting at 10–20mg once a day).

2.2.2. Observation group

PCI surgical treatment was implemented based on conventional drug treatment. Preoperatively, the condition was stabilized with aspirin and carbamazepine to optimize the preoperative state. PCI surgery was performed through the radial artery route. To ensure anticoagulant effect, 100 U/kg of normal heparin was injected intravenously at the beginning of the procedure, and if the procedure lasted for more than 1 h, an additional 1000 U of heparin was administered every hour. According to the patient's specific lesion condition, the appropriate catheter, guidewire, and balloon were selected, and the stent was implanted precisely into the stenotic site of the coronary artery following the standard operation procedure to restore the blood flow. Post-procedure subcutaneous injections of 5000 U of low molecular heparin were administered daily in two divided doses for 3 to 7 days. Carbamazepine of 90 mg twice daily was continued for at least 12 months, along with aspirin 100 mg daily for long-term maintenance. If there are no contraindications, beta-blockers, angiotensin-converting enzyme inhibitors, and statins were continued to prevent the recurrence of cardiovascular events and improve long-term prognosis.

2.3. Observation indicators

- (1) Comparison of the treatment effects of the two groups of patients:
 - (a) Obvious effect: Chest pain, chest tightness and other symptoms disappear, and the ECG performance returns to normal or significantly improves, the coronary artery stenosis is significantly relieved, and the blood flow returns to normal or close to the normal level.
 - (b) Effective: Symptoms such as chest pain, chest tightness and other symptoms have been reduced, ECG has some improvement compared with the previous, and coronary artery stenosis is reduced, but not completely restored to normal blood flow.
 - (c) Ineffective: the patient's symptoms do not improve significantly, or even appear to worsen. There is no

significant change or deterioration in ECG, and the coronary artery stenosis has not been relieved or has become occluded again.

(2) Cardiac function

Echocardiography was applied to detect the left ventricular function of the patients before and after 3 weeks of treatment, including left ventricular septal end-diastolic thickness (IVPWTd) and left ventricular end-diastolic diameter (LVEDd).

(3) Occurrence of complications

Regular follow-up observations were made to record the occurrence of complications such as cardiac insufficiency, arrhythmia, coronary artery spasm, acute thrombosis, chronic renal impairment, and cardiogenic death during the treatment of the patients. The total incidence rate is calculated as follows (Equation 1):

$$\text{Total incidence rate} = \frac{\text{Number of cases occurring}}{\text{Total number of cases}} \times 100\% \quad (1)$$

2.4. Statistical methods

SPSS 24.0 statistical software was applied to analyze and process the relevant data. Measured data were expressed as mean \pm standard deviation (SD) and compared with t-test; count data were expressed as n and compared with χ^2 test. $P < 0.05$ was used to indicate that the difference was statistically significant.

3. Results

3.1. Comparison of clinical efficacy between the two groups of patients

The treatment effective rate of the observation group (98.33%) was significantly higher than that of the control group (86.67%), and the difference was statistically significant ($P < 0.05$). See Table 1.

Table 1. Comparison of clinical outcomes between the two groups (n, %)

Groups	Obvious effect	Effective	Ineffective	Overall effectiveness rate
Control group ($n = 60$)	38 (63.33)	14 (23.33)	8 (13.33)	52 (86.67)
Observation group ($n = 60$)	47 (78.33)	12 (20.00)	1 (1.67)	59 (98.33)
χ^2				4.324
P				0.038

3.2. Comparison of left ventricular cardiac function between the two groups of patients before and after treatment

Before treatment, the difference between the IVPWTd and LVEDd indexes of the two groups of patients was not statistically significant ($P > 0.05$). After 3 weeks of treatment, all the indexes of the two groups of patients decreased significantly, and the observation group was lower than the control group, and the difference was statistically significant ($P < 0.05$), see Table 2.

Table 2. Comparison of left ventricular cardiac function before and after treatment in the two groups (mean \pm SD, mm)

Groups	IVPWTd		LVEDD	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group ($n = 60$)	10.39 \pm 0.86	9.76 \pm 0.62	55.36 \pm 5.67	53.28 \pm 5.63
Observation group ($n = 60$)	10.41 \pm 0.78	8.56 \pm 0.49	56.01 \pm 6.80	49.65 \pm 5.47
t	0.133	11.762	0.569	3.582
p	0.894	0.000	0.571	0.001

3.3. Comparison of the occurrence of complications between the two groups of patients

In terms of the complication rates of cardiac insufficiency, arrhythmia, coronary artery spasm, acute thrombosis, chronic renal impairment, and cardiogenic death occurring during the treatment period of the two groups, the observation group (3.33%) was significantly lower than that of the control group (15.00%), and the difference was statistically significant ($P < 0.05$), as shown in Table 3.

Table 3. Comparison of the difference in complication rates between the two groups (n, %)

Groups	Cardiac insufficiency	Arrhythmia	Coronary spasm	Acute thrombosis	Chronic renal impairment	Cardiac death	Total incidence
Control group ($n = 60$)	1	3	2	1	1	1	9 (15.00)
Observation group ($n = 60$)	0	1	1	0	0	0	2 (3.33)
χ^2							4.904
p							0.027

4. Discussion

Chronic Coronary Syndrome (CCS) is a class of cardiovascular diseases based on coronary atherosclerosis, and its pathological mechanisms mainly include atherosclerotic plaque formation in coronary arteries, reduced plaque stability, inflammatory reaction of the vascular wall, and endothelial dysfunction, which results in coronary blood flow restriction. The myocardium is unable to obtain sufficient blood supply during exercise or emotional excitement, thus triggering ischaemic symptoms, manifested as angina pectoris, chest tightness, etc. [6] As the disease progresses, some patients may deteriorate into acute coronary syndromes (e.g. myocardial infarction). Currently, the treatment of CCS mainly includes drug therapy and percutaneous coronary intervention (PCI). The goals of pharmacological therapy for chronic coronary syndrome are mainly to relieve myocardial ischaemia symptoms, prevent plaque rupture and reduce cardiovascular events [7]. Specific medications include antiplatelet agents (e.g., aspirin, carbamazepine), beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and statins. Antiplatelet drugs can inhibit thrombosis and prevent acute occlusion of coronary arteries; β -blockers can slow down the heart rate, reduce myocardial oxygen consumption, and relieve angina symptoms; ACEIs inhibit the production of angiotensin II, reduce the cardiac load, and improve the function of the vascular endothelium; and statins reduce LDL cholesterol, which can stabilize plaques and prevent them from rupturing [8]. However, drug therapy has certain limitations, and can only improve symptoms and prevent cardiovascular events to maintain the stability of the disease, but cannot completely solve the problem of coronary artery stenosis, if long-term use of antiplatelet drugs and other drugs, not only the emergence of drug resistance or side effects, but also increase the

risk of bleeding^[9].

Percutaneous Coronary Intervention (PCI) has been commonly used in recent years as a minimally invasive interventional solution for the treatment of coronary artery stenosis or occlusion. Its basic principle is to implant a balloon or stent into a narrowed coronary artery through catheter technology to dilate the blood vessel and maintain the lumen of the blood vessel open, restoring the blood supply to the heart muscle and providing rapid relief to the patient. Besides, it can also improve their myocardial ischaemic status and minimize the risk of cardiovascular events.

The results of this study showed that the observation group of patients treated with percutaneous coronary intervention was significantly better than the control group of patients treated with conventional medication in terms of treatment efficiency, IVPWTd, LVEDd levels and the incidence of related complications, etc. The reason for this is that PCI can directly and rapidly relieve coronary artery stenosis and restore myocardial blood supply, thus improving myocardial ischemia, rapidly relieving chest pain and symptoms, improving cardiac function, greatly improving IVPWTd and LVEDd levels. Cardiovascular events and complications can be reduced, improving the overall treatment effect^[10]. Meanwhile, PCI can prevent coronary restenosis more effectively by keeping the vessels open through stent implantation, especially for patients with heavy plaque load or complex lesions.

5. Conclusion

In summary, PCI has a significant effect in improving the symptoms of patients with chronic coronary syndrome, effectively restoring myocardial blood supply, relieving chest pain and other uncomfortable symptoms, and at the same time significantly reducing the risk of complications such as cardiac insufficiency, arrhythmia, and coronary artery spasm, and improving the overall therapeutic effect of patients. However, due to the small sample size included in this study and the relatively short postoperative follow-up period, the long-term efficacy has not been fully clarified. Future studies should expand the sample size, extend the follow-up time, and systematically evaluate the long-term efficacy and safety of PCI, to provide a more adequate basis for clinical practice and further establish its important position in the treatment of chronic coronary syndromes.

Disclosure statement

The authors declare no conflict of interest.

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Study on the Application of Percutaneous Coronary Intervention in Patients with Chronic Coronary Syndrome Combined with Renal Disease

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Abstract: Objective: To analyze the clinical effect of percutaneous coronary intervention in the treatment of chronic coronary syndrome combined with kidney disease. Methods: 150 patients with chronic coronary syndrome combined with renal disease admitted to a hospital from June 2023 to May 2024 were selected, and were divided into the control group and the observation group, 75 cases each, using the mean score method. The control group implemented conventional drug (clopidogrel, aspirin, statins) treatment, and the observation group implemented percutaneous coronary intervention on this basis, comparing the two groups' treatment effects. Results: The mortality rate (9.33%) and the deterioration rate of renal function (5.33%) of patients in the observation group during the treatment period were significantly lower than those of the control group (21.33%) and (16.00%). The average hospitalization time of patients in the observation group was shorter than that of the control group (15.75 ± 4.24) days. The recurrence rate of angina pectoris of the patients of the observation group in the three months after discharge from the hospital was lower than that of the control group (25.33%) and that of the observation group was lower than that of the control group (6.67%), the difference was statistically significant ($P < 0.05$). Before treatment, there was no statistically significant difference in the levels of LVEDD, LVESD, and LVEF between the two groups ($P > 0.05$). After three months of treatment, the LVEDD (52.55 ± 4.02) mm and LVESD (41.44 ± 2.17) mm in the patients of the observation group were lower than those of the control group (57.37 ± 3.74) mm and (46.44 ± 2.59) mm; LVEF (50.78 ± 5.97)% of patients in the observation group was higher than that of (43.06 ± 5.92)% in the control group, and the difference was statistically significant ($P < 0.05$). Before treatment, there was no statistically significant difference in the levels of CK-MB and cTnI between the two groups ($P > 0.05$). At 24h and 72h after treatment, the levels of CK-MB and cTnI in patients of the observation group and the control group were (35.21 ± 9.81) U/L, (1.24 ± 0.34) μ g/L, (13.19 ± 5.12) U/L, (0.36 ± 0.08) μ g/L and (38.79 ± 10.84) U/L, (1.45 ± 0.32) μ g/L, (19.87 ± 4.76) μ g/L, (0.58 ± 0.11) μ g/L, the difference was statistically significant ($P < 0.05$). Conclusion: Percutaneous coronary intervention is effective in treating chronic coronary syndrome combined with renal disease, which can significantly improve the level of a patient's cardiac function and reduce the level of CK-MB and cTnI, and is worth being widely used in clinical practice.

Keywords: Chronic Coronary Syndrome (CCS); Chronic Kidney Disease (CKD); PCI; Cardiac function

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1. Introduction

Chronic Coronary Syndrome (CCS) is a clinical syndrome in which atherosclerotic plaques in coronary arteries gradually increase in size, leading to narrowing of the lumen of coronary vessels and causing myocardial ischemia or angina ^[1]. Chronic kidney disease (CKD) patients often have a higher incidence of coronary atherosclerosis-related lesions due to hypertension, diabetes and chronic inflammation. The conventional treatment for patients with chronic coronary syndrome combined with renal disease is pharmacotherapy, which mainly uses clopidogrel, aspirin and statins to inhibit platelet aggregation, reduce thrombosis, and lower the level of low-density lipoprotein cholesterol, thus decreasing the incidence of restenosis in coronary arteries ^[2]. However, patients with the combined renal disease face increased adverse drug reactions due to decreased renal function and slower drug metabolism and are prone to deterioration of renal function, recurrence of angina pectoris, decrease in left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD), which is the most common cause of coronary artery restenosis. Therefore, ways to optimize the treatment plan for patients with chronic coronary syndromes combined with renal disease, and to reduce the risk of surgical complications and postoperative cardiovascular events have become the focus of clinical attention ^[3]. Percutaneous Coronary Intervention (PCI) has been an important means of clinical treatment for coronary artery disease in recent years, mainly through dilating stenotic coronary arteries, restoring blood flow, alleviating myocardial ischemia, and improving the prognosis of patients. In this study, PCI was applied to patients with CCS combined with CKD, aiming to understand the effect of PCI on the recent prognosis of these patients to provide a scientific basis for the clinical treatment of these patients.

2. Information and methods

2.1. General information

In this study, 150 patients with Chronic Coronary Syndrome (CCS) combined with renal disease who were treated in an institution between June 2023 and May 2024 were selected for the study, all of whom met the diagnostic criteria for Chronic Coronary Syndrome (CCS) and Chronic Kidney Disease (CKD), and all of whom were diagnosed through a joint consultation between cardiovascular medicine and nephrology. The diagnosis was confirmed. They were divided into the control and observation groups using the mean score method, each with 75 cases. The average age of the patients in the control group was (62.3 ± 10.2) years old, of which 45 were male and 30 were female; the average age of the patients in the observation group was (63.1 ± 9.8) years old, of which 47 were male and 28 were female. The differences between the two groups in terms of general clinical data such as gender composition, age, degree of coronary artery lesions, and renal function (assessed according to glomerular filtration rate GFR) were not statistically significant ($P > 0.05$) and were comparable.

Inclusion criteria: (1) age between 18 and 75 years old; (2) confirmed diagnosis of chronic coronary syndrome and the presence of coronary stenosis confirmed by coronary angiography; (3) accompanied by Chronic Kidney Disease (CKD), patients with stage CKD1 to 4 according to glomerular filtration rate (GFR) classification.

Exclusion criteria: (1) patients with a history of acute renal failure; (2) patients with severe hepatic impairment, malignant tumors, immune system disorders or coagulation disorders; (3) patients with recent acute myocardial infarction or severe heart failure.

2.2. Methodology

2.2.1. Control group

The conventional drug treatment program was implemented. After admission, patients are given a series of drugs such as clopidogrel, aspirin, statin, β -blocker, low molecular weight heparin calcium, nitrate lipid preparation,

angiotensin-converting enzyme inhibitor and so on after relevant examinations to exclude contraindications. The treatment program lasted for 1 week, during which the patient's condition was closely monitored, and the type or dose of drugs was adjusted individually according to the patient's clinical response, blood biochemical indexes, and other examination results, to ensure that the therapeutic effect was maximized, the patient's condition was improved as much as possible, and the cardiovascular function was stabilized.

2.2.2. Observation group

PCI surgical treatment was implemented based on conventional drug treatment. Patients were treated with interventional surgery 7–14 days after hospitalization, and individual cases needed to implement emergency interventional therapy. Before the operation, patients routinely take oral aspirin 300 mg/d, take 300 mg clopidogrel within 24 h before the operation, and inject 8000 U heparin via the right side of the radial artery before the intervention. During the procedure, the surgeon selects the appropriate catheter, guide wire, and balloon based on the results of coronary angiography and installs the stent in principle. After the procedure, the patient is required to continue to take 100–325 mg of aspirin daily, 25 mg of OxyContin each time, and after three consecutive months, 100 mg/d of aspirin alone. In addition, platelet glycoprotein IIb/IIIa receptor antagonists are also administered at the appropriate time, depending on the patient's risk of acute thrombosis within the stent to prevent thrombus formation. Throughout the process, the patient's response and recovery need to be closely monitored to ensure optimization of safety and therapeutic efficacy.

2.3. Observation indicators

- (1) Observe and record the death, deterioration of renal function, average hospitalization time and recurrence of angina pectoris at 3 months after discharge during the treatment period of the two groups of patients.
- (2) Use cardiac ultrasound (GE color ultrasound diagnostic instrument PHILIPSC5-1) diagnostic instrument to detect the left ventricular ejection fraction (LVEF), left ventricular end-diastolic internal diameter (LVEDD), left ventricular systolic internal diameter (LVESD) and other levels of cardiac function of the patients in the two groups before the treatment and after 3 months of treatment.
- (3) Comparative analysis of the levels of creatine kinase isozyme (CK-MB) and troponin (cTnI) in the two groups before treatment and 24 h and 72 h after treatment.

2.4. Statistical methods

SPSS 24.0 statistical software was applied to analyze and process the relevant data. Measured data were expressed as mean \pm standard deviation (SD) and compared with t-test, and count data were expressed as n and compared with χ^2 test. $P < 0.05$ was used to indicate that the difference was statistically significant.

3. Results

3.1. Comparison of prognosis between the two groups

The mortality rate and renal function deterioration rate of patients in the observation group during the treatment period were significantly lower than those of the control group, the average hospitalization time was shorter than that of the control group, and the angina recurrence rate at three months after discharge was lower than that of the control group, and the difference was statistically significant ($P < 0.05$), as shown in Table 1.

Table 1. Comparison of the prognosis of the two groups of patients

Group	Deaths during hospitalization (n, %)	Deterioration of renal function during hospitalization (n, %)	Average length of hospitalization (d)	Recurrence of angina 3 months after discharge (n, %)
Control group (<i>n</i> = 75)	16 (21.33)	12 (16.00)	15.75 ± 4.24	19 (25.33)
Observation group (<i>n</i> = 75)	7 (9.33)	4 (5.33)	11.86 ± 3.18	5 (6.67)
χ^2 / <i>t</i>	41.9254	51.9552	6.3563	42.6393
<i>p</i>	0.0000	0.0000	0.0000	0.0000

3.2. Comparison of cardiac function levels between the two groups before and after treatment

Before treatment, there was no statistically significant difference in the levels of LVEDD, LVESD and LVEF between the two groups ($P > 0.05$), and after 3 months of treatment, LVEDD and LVESD in the observation group were lower than those in the control group, and LVEF was higher than those in the control group, and the difference was statistically significant ($P < 0.05$), as shown in Table 2.

Table 2. Comparison of cardiac function levels before and after treatment in the two groups (mean ±SD)

Group	LVEDD (mm)		LVESD (mm)		LVEF (%)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group (<i>n</i> = 75)	62.45 ± 4.16	57.37 ± 3.74	51.49 ± 4.78	46.44 ± 2.59	33.61 ± 4.31	43.06 ± 5.92
Observation group (<i>n</i> = 75)	62.43 ± 4.22	52.55 ± 4.02	52.06 ± 3.55	41.44 ± 2.17	33.28 ± 4.16	50.78 ± 5.97
<i>t</i>	0.0292	7.6024	0.8291	12.8152	0.4771	7.9520
<i>p</i>	0.9767	0.0000	0.4084	0.0000	0.6340	0.0000

3.3. Comparison of CK-MB and cTnI levels in two groups of patients

Before treatment, there was no statistically significant difference in the levels of CK-MB and cTnI between the two groups ($P > 0.05$). at 24 h and 72 h after treatment, the levels of CK-MB and cTnI in patients of the observation group were significantly lower than those in the control group, and the difference was statistically significant ($P < 0.05$), as shown in Table 3.

Table 3. Comparison of CK-MB and cTnI levels before and after treatment in the two groups (mean ± SD)

Group	CK-MB (U/L)			cTnI (μg/L)		
	Pre-treatment	24 h after treatment	72 h after treatment	Pre-treatment	24 h after treatment	72 h after treatment
Control group (<i>n</i> = 75)	40.24 ± 12.55	38.79 ± 10.84	19.87 ± 4.76	1.68 ± 0.67	1.45 ± 0.32	0.58 ± 0.11
Observation group (<i>n</i> = 75)	39.74 ± 13.12	35.21 ± 9.81	13.19 ± 5.12	1.70 ± 0.66	1.24 ± 0.34	0.36 ± 0.08
<i>t</i>	0.2385	2.1207	8.2752	0.1842	3.8951	14.0077
<i>p</i>	0.8118	0.0356	0.0000	0.8541	0.0001	0.0000

4. Discussion

4.1. Causes of increased morbidity and mortality in patients with 1CKD combined with CCS

Currently, cardiovascular disease and chronic kidney disease (CKD) pose a major threat to global health, and the link between the two is strong, on the one hand, chronic kidney disease (CKD) is an important independent risk factor for the deterioration of cardiovascular disease on the other hand, coronary artery disease is one of the main causes of complications and death in patients with CKD ^[4]. The interaction of these two diseases leads to a higher mortality rate of patients during hospitalization and the analysis of the causes can be attributed to several factors:

- (1) Patients may present with atypical symptoms, leading to delays in diagnosis and treatment, thus missing critical treatment opportunities ^[5].
- (2) Patients tend to have severe coronary artery lesions, which are extensive and accompanied by severe arterial calcification, thus exacerbating the risk of cardiovascular events.
- (3) Patients during hospitalization face a higher risk of in-hospital hemorrhage, stroke, further deterioration of renal function, and cardiogenic shock, further increasing the difficulty of treatment and mortality ^[6].

Therefore, treatment strategies for such patients need to be more careful and thoughtful to reduce complications and improve survival.

4.2. Prognosis and impact of interventional therapy on ACS patients with comorbid CKD

Interventional therapy can significantly affect the prognosis of patients with chronic coronary syndromes (CCS) who have comorbid chronic kidney disease (CKD). Immediate and long-term outcomes after PCI in patients with CKD are usually more complicated compared with those without CKD. CKD itself is an independent risk factor for cardiovascular disease. When ACS occurs in these patients, their vessel walls often already have more severe calcification and stenosis, which not only increases the technical difficulty of the intervention but also increases the risk of complications such as vascular injury and thrombosis ^[7]. However, despite these risks, most studies have shown that prompt PCI improves short and long-term prognosis in CCS patients with comorbid CKD. The intervention provides rapid flow reconstruction, which can effectively reduce the area of myocardial infarction and reduce the ischemic burden on the heart, thereby improving cardiac function and quality of life. PCI addresses the physical obstruction of the coronary arteries more directly and provides more stable blood flow restoration than pharmacologic therapy ^[8]. However, the use of contrast media in CKD patients undergoing PCI can exacerbate renal injury. Therefore, careful assessment of renal function and precautionary measures, such as the use of renal-protective contrast media, limiting the total amount of contrast media, and ensuring adequate fluid supplementation, are needed to prevent restenosis and other cardiovascular events before intervention.

4.3. Effects on renal function

Blood creatinine level is a biochemical indicator commonly used to assess renal function; however, it is affected by a variety of physiological factors such as gender, age, and muscle mass in the body, resulting in that it may not always accurately reflect the degree of renal impairment in early kidney injury. Especially in the elderly, blood creatinine level fails to truly reflect the actual state of renal function due to generally low muscle mass, which becomes an important reason for the low diagnosis rate of chronic kidney disease (CKD) in the clinic ^[9]. Renal function assessment is particularly important in the clinical management of chronic coronary syndrome (CCS). Decreased levels of renal function can exacerbate a patient's overall condition, especially when cardiovascular events such as ACS occur. If a patient undergoes percutaneous coronary intervention (PCI), the use of contrast agents can further exacerbate renal injury and trigger acute renal failure, which is particularly common in patients with comorbid CKD. The incidence of postprocedural acute renal function deterioration is significantly higher in

this specific patient population than in patients with common ACS. Therefore, when treating this group of patients, it is important to find a balance between aggressive interventional therapy and its potential risk to renal function^[10].

5. Conclusion

In summary, in CCS patients with comorbid CKD, percutaneous coronary intervention (PCI) will not only reduce the risk of deterioration of renal function during hospitalization but will also reduce overall in-hospital mortality. However, it is worth noting that the risk of both deterioration of renal function and death remains higher in this specific patient population than in the general population of patients with ACS. Therefore, when PCI or other therapeutic options are undertaken, the potential risks and prognosis need to be explained in detail to patients and their families, and a thorough assessment and planning needs to be undertaken to ensure the overall health and quality of life of the patient.

Disclosure statement

The authors declare no conflict of interest.

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Study on the Effect of LEARNS Model in Self-Management of Patients with Maintenance Hemodialysis and Volume Overload

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Abstract: *Objective:* To investigate the effect of the LEARNS model in the self-management of patients with maintenance hemodialysis and volume overload. *Methods:* Eighty patients with maintenance hemodialysis and volume overload admitted from September 2022 to May 2024 were selected as the main subjects of this experiment. They were divided into two groups based on the odd or even days of their admission, with 40 patients in each group. Patients admitted on odd days were included in the new group and received LEARNS model education, while patients admitted on even days were included in the traditional group and received traditional education. The self-care ability, treatment adherence, and quality of life were compared between the new group and the traditional group. *Results:* The self-care ability, treatment adherence, and quality of life of patients with maintenance hemodialysis and volume overload in the new group were significantly higher than those in the traditional group, with statistically significant differences between the groups ($P < 0.05$). *Conclusion:* The LEARNS model is more effective in the self-management of patients with maintenance hemodialysis and volume overload, and it is worthy of widespread clinical application.

Keywords: LEARNS model; Maintenance hemodialysis; Self-management; Treatment adherence; Quality of life

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1. Introduction

Maintenance hemodialysis is the primary clinical treatment for end-stage renal disease. It involves the use of a hemodialysis machine to remove toxins, excess water, and metabolic waste from the body, thereby extending patients' survival and reducing mortality rates^[1]. However, long-term hemodialysis often leads to a series of complications, resulting in strong negative emotions and a significant reduction in patients' quality of life. Among these, volume overload is a common complication for hemodialysis patients and a significant contributor to cardiovascular events. Therefore, effective interventions are necessary, including health education to improve patients' disease awareness, compliance, and cooperation. Currently, reports are indicating the significant

effectiveness of the LEARNS model in self-management for patients with volume overload undergoing maintenance hemodialysis ^[2]. To verify this, the study selected 80 patients with volume overload undergoing maintenance hemodialysis admitted between September 2022 and May 2024 as the main subjects for this study. They were divided into two groups based on their admission dates: 40 patients admitted on odd-numbered days were included in the novel group and received LEARNS model education, while 40 patients admitted on even-numbered days were included in the traditional group and received traditional education. The study compared the self-care ability, treatment compliance, and quality of life between the two groups.

2. Materials and methods

2.1. Basic information

80 patients with maintenance hemodialysis and volume overload, admitted between September 2022 and May 2024, were selected as the primary subjects for this experiment. They were divided into two groups based on whether they were admitted on an odd or even day of the month, with 40 patients in each group. Patients admitted on odd days were included in the novel group and underwent LEARNS mode education, while those admitted on even days were included in the traditional group and received traditional education. The traditional group consisted of 22 male patients and 18 female patients, with ages ranging from 27 to 65 years old, and an average age of (43.66 ± 2.17) years old. The novel group comprised 23 male patients and 17 female patients, aged between 28 and 63 years old, with a mean age of (43.88 ± 2.63) years old. The basic characteristics of the study subjects were comparable ($P > 0.05$).

Inclusion criteria: The experimental content was approved by the ethics committee. The subjects met the criteria for maintenance hemodialysis ^[3], were confirmed by pathological examination, were aware of the experimental procedures, and agreed to the experimental content.

Exclusion criteria: Pregnant or breastfeeding patients; patients with organ dysfunction; patients with comorbidities such as malignant tumors, immune diseases, infectious diseases, or mental illnesses ^[4].

2.2. Methods

The traditional group underwent routine education, where patients were guided on a scientific diet and correct medication usage through oral instruction. Detailed explanations were provided on the precautions and complications during hemodialysis. Each session lasted for 40 minutes, twice a week, for a total of 6 weeks.

The novel group implemented the LEARNS model. Firstly, an education team was formed, consisting of 1 physician responsible for developing and improving nursing content, 1 nurse practitioner as the team leader in charge of overall management, 2 head nurses responsible for supervising the implementation of the program, and 6 nurses tasked with executing the LEARNS model.

In addition, the implementation of the LEARNS model began with:

- (1) Listening (L): Questions were posed to patients based on a prepared interview outline, including inquiries about the meaning of hemodialysis, possible complications after hemodialysis, and methods to control dry weight. This allowed for a comprehensive understanding of the patient's disease cognition, assessment and organization of their information needs, and attention to ease their negative emotions. During this period, the focus was primarily on listening and observing the patient's emotional and physical changes to ensure their comfort.
- (2) Establishment (E): Based on interview information, develop an educational plan. After the plan is approved, schedule an education session with the patient, implement the health education according to the plan, patiently answer the patient's questions, and pay attention to communication skills.

- (3) Application and Improvement (A and R): Conduct centralized oral education by explaining hemodialysis knowledge based on the patient's needs and preferences, such as dry weight management methods, exercise and diet management, and hypotension prevention techniques. Focus on two key topics per session, with each session lasting one hour for a total of four weeks. Additionally, utilize video education by creating health knowledge promotional videos tailored to patients' needs and sending them via WeChat for easy learning and understanding. This includes topics like internal fistula care methods and skin itching treatment techniques.
- (4) Feedback Teaching (N): After the education session, ask patients questions based on the previous health education content, such as dry weight control methods and internal fistula arm exercise techniques. Identify any areas of confusion or misunderstanding and improve based on the patient's knowledge mastery to enhance their understanding of the disease.
- (5) Reinforcement (S): Reinforce education on easily confused topics by utilizing patients' fragmented time for face-to-face guidance, achieving one-on-one education.

2.3. Evaluation criteria

- (1) The ESEA rating scale is used to evaluate patients' self-care abilities, including four dimensions and 43 items: Health knowledge level, self-concept, self-responsibility, and self-care skills. Each item is rated from 0 to 4, with a total score ranging from 0 to 172. A higher score indicates stronger self-care abilities^[6].
- (2) A self-made questionnaire is used to analyze patients' treatment adherence, with independent scoring by the patients themselves. The total score is 10, where a score greater than 7 indicates adherence, a score between 3 and 7 indicates partial adherence and a score less than 3 indicates non-adherence. The total adherence rate is calculated as (total number of adherent cases) \times 100%^[7].
- (3) The sf-36 rating scale is used to evaluate patients' quality of life, including eight dimensions. The score for each dimension is calculated as (actual score for the dimension / theoretical total score) \times 100. A higher score indicates a better quality of life for the patient^[8].
- (4) A self-made questionnaire is used to analyze patients' satisfaction with nursing care, with independent scoring by the patients themselves. The total score is 10, where a score greater than 7 indicates satisfaction, a score between 3 and 7 indicates partial satisfaction and a score less than 3 indicates dissatisfaction. The total satisfaction rate is calculated as (total number of satisfied cases) \times 100%^[9].

2.4. Statistical methods

Using the SPSS 26.0 system, enumeration data was represented by (*n*, %), and the chi-squared test was conducted; measurement data was represented by mean \pm standard deviation (SD), and the *t*-test was conducted. The test level was set at $P < 0.05$.

3. Results

3.1. Comparison of self-care abilities between the traditional group and the new group

Comparing self-care abilities between the traditional group and the new group, the total self-care score of the new group was significantly higher than that of the traditional group, and the difference between the groups was statistically significant ($P < 0.05$) (Table 1).

Table 1. Comparing self-care abilities between the traditional group and the new group (mean \pm SD, scores)

Group/Number of cases	Health knowledge level	Self-concept	Self-responsibility	Self-care skills	Total self-care score
New group ($n = 40$)	44.51 \pm 8.53	20.06 \pm 5.27	15.47 \pm 3.39	27.36 \pm 5.51	114.55 \pm 20.11
Traditional group ($n = 40$)	40.06 \pm 5.46	15.17 \pm 5.74	13.65 \pm 3.16	23.59 \pm 6.27	96.22 \pm 18.16
<i>T</i> value	5.382	4.066	3.046	4.163	10.472
<i>P</i> -value	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

3.2. Comparison of treatment compliance between the traditional group and the new group

The overall treatment compliance rate in the new group was 92.50%, which was significantly higher than the 75.00% compliance rate in the traditional group. The difference between the two groups was statistically significant ($P < 0.05$) (Table 2).

Table 2. Treatment compliance of patients in the traditional group and the new group [$n(\%)$]

Group/Number of cases	Compliant	Fairly compliant	Non-compliant	Total compliance rate
New group ($n = 40$)	17	20	3	37 (92.50)
Traditional group ($n = 40$)	14	16	10	30 (75.00)
χ^2 value				5.074
<i>P</i> -value				< 0.05

3.3. Comparison of quality of life between traditional and new group patients

Before treatment, there was no significant difference in the quality of life between the traditional group and the new group ($P > 0.05$). After treatment, the quality of life improved in both groups, with the new group showing significantly higher scores than the traditional group. The difference was statistically significant ($P < 0.05$) (Table 3).

Table 3. Comparison of quality of life between traditional and new group patients (points)

Group/Number of cases	Social function (SF)		Vitality (VT)		Physiological function (PF)		Mental health (MH)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
New group ($n = 40$)	68.27 \pm 8.54	91.07 \pm 9.64	71.66 \pm 2.87	93.47 \pm 3.82	70.16 \pm 2.45	92.75 \pm 3.55	70.47 \pm 1.36	93.85 \pm 3.16
Traditional group ($n = 40$)	67.27 \pm 8.33	81.11 \pm 7.33	71.47 \pm 1.36	81.46 \pm 2.16	67.33 \pm 4.32	83.22 \pm 3.14	69.48 \pm 5.22	82.44 \pm 4.55
<i>T</i> value	0.342	3.124	0.363	3.667	0.235	5.514	0.537	6.106
<i>P</i> -value	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05
Group/Number of cases	Bodily pain (BP)		General health (CH)		Role emotional (RE)		Role physical (RP)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
New group ($n = 40$)	68.74 \pm 3.61	94.95 \pm 1.48	65.85 \pm 5.73	89.59 \pm 7.74	69.06 \pm 6.67	88.64 \pm 7.06	68.06 \pm 7.59	88.45 \pm 7.47
Traditional group ($n = 40$)	68.38 \pm 2.48	79.37 \pm 5.69	65.84 \pm 4.27	81.06 \pm 6.62	70.47 \pm 5.18	80.57 \pm 6.18	70.63 \pm 5.28	81.67 \pm 6.87
<i>T</i> value	0.473	5.234	0.352	6.327	0.584	6.097	0.259	5.286
<i>P</i> -value	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05

4. Discussion

Hemodialysis is one of the safer, more feasible, and widely used blood purification methods, which has certain significance in reducing patients' symptoms and prolonging their survival. To improve the self-management ability of patients with maintenance hemodialysis and volume overload, it is imperative to implement modern nursing methods ^[11].

The LEARNS model, as a progressive health education model, helps to enhance patients' awareness of hemodialysis knowledge, improve their self-care skills, and meet their diversified health knowledge needs. By patiently listening and establishing a cooperative partnership with patients, conducting WeChat interactions during the application and improvement stages, and launching educational activities through a combination of online and offline methods, patients' questions can be answered promptly. The feedback and reinforcement stages can effectively correct patients' misconceptions about hemodialysis knowledge, deepen their memory, strengthen their mastery of health knowledge, and increase their interest in learning ^[12]. The experimental results of this paper show that the total self-care score of the new group is significantly higher than that of the traditional group, and the difference between the groups is statistically significant ($P < 0.05$). The total treatment compliance rate of the new group is 92.50%, which is significantly higher than the 75.00% of the traditional group, and the difference between the groups is statistically significant ($P < 0.05$). Before the intervention, there was no significant difference in quality of life between the traditional group and the new group ($P > 0.05$); after the intervention, the quality of life of both groups improved, and the quality of life score of the new group was significantly higher than that of the traditional group, with a statistically significant difference ($P < 0.05$). These findings are almost consistent with previous research conclusions ^[13–15], fully demonstrating the effectiveness of the LEARNS model in the self-management of patients with maintenance hemodialysis and volume overload, and also validating the value of this experiment.

5. Conclusion

In summary, the LEARNS model has a more prominent effect on the self-management of patients with maintenance hemodialysis and volume overload. It improves self-care ability and treatment compliance while enhancing the quality of life, making it worthy of widespread clinical application.

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Analysis of a Case of Immune-Related Myocarditis Combined with Myasthenia Gravis and Liver Injury Induced by Tislelizumab

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Abstract: Immune checkpoint inhibitors (ICIs) have demonstrated significant advantages and potential in tumor immunotherapy, but immune-related adverse events (irAEs) are becoming increasingly important safety issues. This article analyzes and discusses a case of a patient with esophageal cancer who developed bilateral lower limb weakness, bilateral ptosis, loss of appetite, nausea, and vomiting after four cycles of treatment with tislelizumab. The patient was considered to have immune-related myocarditis, myasthenia gravis, and liver injury involving multiple organs caused by tislelizumab treatment. As multi-organ damage caused by tislelizumab is rarely reported domestically and internationally, this article will analyze and discuss domestic and foreign literature, hoping to provide some help to clinicians who subsequently use tislelizumab.

Keywords: Immune checkpoint inhibitors; Immune-related adverse reactions; Myocarditis; Myasthenia gravis; Liver injury

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1. Introduction

In recent years, immune checkpoint inhibitors (ICIs) have been used to treat various types of tumors. Programmed death-1 (PD-1) and programmed death ligand 1 (PD-L1) immune checkpoint inhibitors represent one of the most important breakthroughs in the treatment of advanced malignancies^[1]. However, they can potentially cause a series of unique side effects, known as immune-related adverse events (irAEs)^[1,2]. irAEs include skin, gastrointestinal, liver, endocrine events, and other uncommon inflammatory events. Although uncommon, ICIs can cause fulminant and even fatal toxic reactions^[3]. Therefore, irAEs must be identified and managed promptly. This article reports a case of multi-organ irAEs: myocarditis, myasthenia gravis, and liver injury, that occurred in a patient with advanced esophageal cancer after the application of tislelizumab. The patient's symptoms did not improve after glucocorticoid treatment, ultimately leading to death. The study will summarize the clinical characteristics and treatment strategies of immune-related multi-organ damage caused by ICI inhibitors, hoping to provide references for the prevention and management of clinically relevant adverse reactions.

2. Case information

The patient, a 69-year-old male, presented with symptoms of nausea and vomiting in March 2022. A gastroscopy was performed, and a biopsy was taken, although the pathological results were not detailed. On July 6, 2022, the patient underwent radical surgery for esophageal cancer, followed by three cycles of immunotherapy combined with chemotherapy using Tislelizumab, Albumin-bound Paclitaxel, and Cisplatin. The patient underwent a fourth cycle of chemotherapy on November 5, 2022, with Tislelizumab (200 mg), Albumin-bound Paclitaxel (400 mg), and Cisplatin (40 mg). The process went smoothly without any significant adverse reactions.

On November 27, 2022, the patient woke up to find bilateral eyelid ptosis and weakness in lifting, which was more pronounced in the evening than in the morning. He also experienced nausea, vomiting, a slightly hoarse voice, intermittent spitting of white mucus, double vision, weakness in both lower limbs, and poor appetite, but denied having headaches, palpitations, chest tightness, or chest pain. Past medical history includes a 14-year history of diabetes mellitus, treated with Metformin Sustained-Release Tablets and Gliclazide Sustained-Release Tablets, with controllable blood glucose levels. The patient denied having hypertension, coronary heart disease, cerebrovascular disease, hepatitis, or any other relevant medical history. There is no significant family history or history of drug or food allergies.

On December 1, 2022, a physical examination was performed upon admission, revealing a temperature of 36.5°C, a heart rate of 110 beats per minute, a respiratory rate of 20 breaths per minute, and a blood pressure of 160/106 mmHg. The patient had a fast heart rate of 110 beats per minute, with a regular rhythm. No significant heart murmurs were heard in the valve auscultation areas. The nervous system examination showed that the patient was conscious, mentally stable, had unclear speech but normal intelligence, bilateral eyelid ptosis, and fixed bilateral eyeballs with limited upward, downward, left, and right gaze. The pupils were 3 mm in diameter, equal in size and round, with a normal pupillary light reflex. The patient had a hoarse voice, dysphonia, normal bilateral pharyngeal reflexes, and no abnormalities in other cranial nerves. The flexor muscle strength of both upper limbs was normal, while the extensor muscle strength was grade 4. The muscle strength of both lower limbs was grade 4. The finger-to-nose test and heel-to-knee-to-shin test were stable and accurate on both sides. The sensation was normal, and tendon reflexes of the extremities were reduced, with negative pathological signs.

Auxiliary examinations were performed on December 1, 2022, including a craniocerebral MRI+MRA, which indicated multiple cerebral ischemic lesions, brain atrophy, craniocerebral arteriosclerosis, and changes in the paranasal sinuses. Laboratory tests showed creatine phosphokinase levels of 3610.0 U/L, lactate dehydrogenase levels of 802.0 U/L, creatine kinase isoenzyme mass of 73.2 µg/L, troponin I levels of 5.51 ng/mL, and B-type natriuretic peptide precursor levels of 2795 pg/mL. Upon urgent examination, the patient showed no significant symptoms such as chest tightness or chest pain, dyspnea or shortness of breath. An electrocardiogram revealed significant ST-segment depression in some leads, and no obvious heart murmurs were heard during the physical examination. Considering acute myocardial damage, the patient was treated with aspirin, ticagrelor dual antiplatelet therapy, statins, and vasodilators.

On the second day of the patient's admission (December 2, 2023), their condition worsened with significant dyspnea, inability to lie flat, persistent bilateral ptosis, slurred speech, increased oral secretions, weakness in all four limbs, decreased muscle strength and reflex, and non-cooperation in gait examination. Electromyography showed damage to the peripheral nerves in both lower limbs. Laboratory tests revealed elevated alanine transaminase (101.8 U/L) and aspartate transaminase (1185.4 U/L). Given the patient's acute onset, previous immunotherapy combined with chemotherapy, and medical history, acute immune-related adverse reactions were suspected, including myocardial injury, liver damage, and severe myasthenia affecting swallowing muscles and eyelids. Therefore, the patient was treated with methylprednisolone sodium succinate 1000 mg qd, recombinant

human brain natriuretic peptide infusion, and nitroglycerin infusion. At approximately 3:30 on December 3, 2023, the patient became unconscious and unresponsive to calls. Physical examination showed equal and round pupils bilaterally with sluggish light reflex, suggesting type II respiratory failure. The patient was intubated and connected to a ventilator for assisted respiration. ECG indicated sinus tachycardia, left axis deviation, and complete left bundle branch block.

On December 4, 2023, the patient's condition remained critical, requiring continuous ventilator-assisted respiration with no signs of dyspnea. Norepinephrine infusion was maintained to stabilize blood pressure, while continuous infusions of butorphanol, propofol, amiodarone, and ulinastatin were administered for sedation, analgesia, ventricular rate control, and reducing cardiac workload, respectively. Laboratory tests showed improved liver function with alanine transaminase at 84.0 U/L and aspartate transaminase at 84.9 U/L, but elevated lactate dehydrogenase (665.0 U/L), creatine phosphokinase (619.0 U/L), creatine kinase isoenzyme mass (5.32 µg/L), N-terminal pro-brain natriuretic peptide (9763 pg/mL), and cardiac troponin I (16.51 ng/mL). The patient continued to receive high-dose corticosteroid therapy with reduced dosage (500 mg/dose qd) and treatments to improve myocardial blood supply, nourish the myocardium, reduce cardiac workload, and enhance cardiac function. However, on December 6, 2023, at 3:08, the patient's blood pressure dropped, and despite aggressive resuscitative efforts, the patient passed away three hours later.

3. Discussion

Tislelizumab is a humanized recombinant monoclonal antibody targeting programmed death receptor (PD)-1, which demonstrates good tolerability and antitumor effects in patients with advanced solid tumors ^[4]. While treating tumors, it may excessively stimulate the body's immune function, leading to multi-system immune-related adverse events (irAEs). Currently, there are reports of myocarditis and myasthenia gravis caused by immune checkpoint inhibitors (ICIs) both domestically and internationally. Although the clinical incidence of such adverse reactions is low, they can cause fulminant and even fatal toxic reactions. This article reports a case of a patient with esophageal cancer who developed myocarditis, myasthenia gravis, and multi-organ damage including liver injury after four cycles of tislelizumab treatment. Clinicians should be vigilant about the occurrence of multi-system damage irAEs during the application of this drug. This aims to remind clinicians to promptly manage patients using ICIs who show symptoms or signs of adverse reactions.

Myocarditis is a rare immune-mediated adverse event. According to previous reports, its incidence is low, ranging from only 0.06% to 1%, but the mortality rate it causes is very high, between 20% and 50% ^[4,5]. Observational studies have also shown that the incidence of myocarditis with combination immunotherapy is higher than that with monotherapy. ICI-related myocarditis manifests in various ways, commonly including shortness of breath, chest pain, and ventricular arrhythmias ^[6]. At the same time, there are also many nonspecific symptoms, such as edema, fatigue, nausea, and myalgia ^[7]. These nonspecific symptoms are atypical and can be easily overlooked, leading to serious consequences.

The pathological mechanism of myocarditis has not been fully elucidated. Some researchers believe that there may be common antigens between tumor cells and cardiomyocytes ^[8]. Another proposed mechanism is the relative weakening of immune tolerance in the periphery of the heart ^[9]. The diagnosis of myocarditis is primarily based on the 2013 European Society of Cardiology Guidelines. Patients presenting with symptoms or signs related to myocarditis should promptly undergo electrocardiography, troponin testing, echocardiography, and cardiac magnetic resonance imaging. Endomyocardial biopsy may be performed if necessary ^[10].

Currently, high-dose glucocorticoids (prednisone 1–2 mg/kgd) are used for pulse therapy in cases of

immune checkpoint inhibitor (ICI)-related myocarditis. However, despite aggressive treatment, the condition may still progress ^[10]. For patients who do not respond immediately to high-dose corticosteroids, a steroid regimen targeting heart transplant rejection (methylprednisolone 1 g/d) should be promptly initiated, along with the addition of mycophenolate mofetil, infliximab, or antithymocyte globulin therapy. In life-threatening cases, immunosuppression with abatacept or alemtuzumab may be added ^[11].

The incidence of ICI-related myasthenia gravis is between 0.1% and 0.2%. It may sometimes occur concurrently with inflammatory myopathy and myocarditis and has a high fatality rate ^[12,13]. Common clinical symptoms include ptosis or diplopia, muscle weakness in the limbs, difficulty breathing, and swallowing. Research on the specific pathogenesis of ICI-related myasthenia gravis is currently very limited. Some studies have found changes in the CD8/CD4 ratio of peripheral blood lymphocytes and inhibition of T-regulatory cell activity ^[14].

In patients with immune checkpoint inhibitor (ICI)-related myasthenia gravis, the positive rate of anti-acetylcholine receptor antibodies ranges from 57% to 83%. Positive results may be observed in the ice pack test and neostigmine test ^[15]. If the patient simultaneously presents with hypercreatinemia, it suggests that the patient may also have ICI-related myositis. Once ICI-related myasthenia gravis occurs, ICI treatment should be immediately discontinued, and corresponding treatment should be administered as soon as possible. ICI-related myasthenia gravis should be treated with glucocorticoids. If symptoms do not improve or worsen after 3 days, plasma exchange and intravenous immunoglobulin should be considered ^[16]. Early identification and intervention are key to reducing the severity and duration of toxicity.

4. Conclusion

This article reports a case of cardiovascular, neurological, and liver injury after four cycles of treatment with Tislelizumab. By summarizing the diagnostic and treatment measures for such adverse reactions at home and abroad, the study aimed to remind clinicians to comprehensively monitor immune indicators in patients receiving ICIs. For patients with multi-organ immune-related adverse events (irAEs) or those with life-threatening complications, early diagnosis and timely glucocorticoid treatment are crucial for prognosis.

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Advances in Identification and Clinical Management Strategies of Nitrate Resistance

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Abstract: Nitrates are widely used in acute and critical diseases such as angina pectoris, acute heart failure and hypertension. However, there are still many problems caused by the non-standard use of these kinds of drugs and drug resistance, which need to be paid attention to in clinical practice, scientific research, and patient education. This article mainly reviews the identification and clinical treatment strategies for nitrate resistance.

Keywords: Nitrates; Drug resistance; Clinical

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1. Introduction

Nitrate drug-resistant patients generally refer to the continuous administration after 24–72 h, the original dose of nitrate ester drugs against myocardial ischemia and enlargement vascular effect decreased or disappeared, patients exercise tolerance or need to increase the dose or share the other measures to maintain the original effect^[1]. Nitrate drug resistant reaction involving the hemodynamic effect, against myocardial ischemia effect, the prognosis of patients with vascular endothelial function, activity, tolerance and aspects can make those of nitrate medications used in the clinical effect of fall, for the treatment of patients with coronary heart disease and other cardiovascular disease cause an adverse effect, this must cause enough attention to clinical and scientific research, and patient education^[2].

2. Mechanisms of resistance to nitrates

The mechanisms of resistance may involve nitrate bioconversion, reduced bioactivity of NO, and activation of counterregulatory mechanisms, such as oxidative stress theory, neurohormone activation theory, mitochondrial dysfunction theory, and sulfhydryl depletion theory. The production of oxidative stress may be an important mechanism of nitrate drug resistance. The increase of reactive oxygen species (ROS) will affect the key enzyme of nitroglycerin (GTN) metabolism, acetaldehyde dehydrogenase 2 (ALDH2), thereby interfering with GTN

bioconversion and NO production ^[3]. In addition, the polymorphism of the *ALDH2* gene can affect the resistance to nitrate. The wild-type (G allele) of the *ALDH2* gene has a normal catalytic activity of GTN, while the mutant (A allele) has a reduced catalytic activity of GTN. Therefore, the *ALDH2* gene mutant population is a potential population of nitrate resistance.

3. Identification methods of nitrate resistance

There are many methods to evaluate nitrate resistance, such as observation of antianginal effect, bicycle exercise test, measurement of peripheral arterial dilatation, forearm plethysmography, measurement of changes in plasma levels of some factors, and direct measurement of coronary artery dilatation. Among them, the observation of the antianginal effect is a widely used evaluation method in clinical work, and a more accurate and intuitive method is to directly measure the degree of coronary artery dilatation before and after drug use under coronary angiography ^[4].

3.1. Identification of clinical manifestations

The clinical effect of each dose of nitrate in patients decreases or disappears, or is accompanied by a decrease in exercise tolerance, and it is necessary to increase the dose or combine other measures (combined with sulfhydryl donor or temporary withdrawal of the drug) to maintain the original effect ^[5].

3.2. Identification of true and false drug resistance

Pseudoresistance refers to drug resistance caused by extravascular factors, which may be related to neuroendocrine feedback regulation and circulating blood volume. Pseudoresistance generally occurs in the early stage of nitrate treatment (24–48 hours), and there is no expected hemodynamic effect on high-dose GTN at the beginning. True resistance refers to resistance caused by vascular factors, including changes in vascular structure and function, which is the most common. It means that the effect of any nitrate agent decreases after 48–72 hours of continuous application, and the drug resistance phenomenon occurs rapidly and disappears after a short withdrawal period (24 hours).

3.3. Identification of cross-resistance

This refers to the emergence of resistance between different drugs or routes of administration, which is manifested as the use of a nitrate drug, reducing the efficacy of different routes, other types of nitrate drugs, NO donor vasodilators or endogenous NO.

3.4. Specific resistance phenomenon

It refers to the same individual different vascular bed resistance, and different system resistance in different organs. In general, resistance occurs first in the venous vascular bed, then in the small arteries, and finally in the large arteries ^[6].

3.5. New identification method: identification of drug-resistant population

The *ALDH2* gene is related to oxidative stress mechanism, hydroxyl depletion theory and other mechanisms. It has gene polymorphism, and the common mutation is glutamic acid in the wild type is replaced by lysine in the mutant type (*Glu487Lys*). Literature reports that the proportion of the wild homozygous type is significantly higher than that of the mutant type in angina pectoris patients in the effective GTN treatment group, and the wild homozygous type has a stronger response to GTN and a faster onset of action. In the Chinese population, according to a study of sublingual only after administering nitrates *ALDH2* genotype of wild crowd reactivity increased cardiac output,

has nothing to do with whether merge coronary heart disease (CHD), which showed that nitrate ester drug curative effect is affected by the *ALDH2* gene significantly ^[7].

There are significant regional and ethnic differences in *ALDH2* gene polymorphisms: the proportion of *ALDH2* mutations with low catalytic activity in the Asian population is significantly higher than that in other regions, up to 40%, especially in the East Asian population. Literature statistics showed that 30–50% of the *ALDH2* gene mutation in the Chinese population, and the mutation rate of the *ALDH2* gene also has regional differences in China. The mutation rate of the Han population in the southeast of Fujian and east of Guangdong is the highest, and it shows a significant downward trend from southeast to northwest.

ALDH2 is not only closely related to the metabolism of GTN but also a key enzyme in the process of alcohol metabolism in the human body ^[8]. The key residue *Cys302* in the enzyme active center plays a crucial role in the catalytic reaction as a nucleophile. Blushes after drinking in the East Asian population are related to the diversity of *ALDH2* dehydrogenase genes. The mutant gene *Glu504Lys* leads to the mutation of *Cys302*, which leads to the severe loss of *ALDH2* activity, leading to the abnormal metabolism of acetaldehyde and the accumulation of acetaldehyde leading to telangiectasia. This population also has abnormal metabolic conversion of GTN to NO. Accepts the patient after asking whether facial redness, after drinking can quickly identify patients may *ALDH2* genotypes, can forecast for the first time as those of nitrate medications curative effect, avoid the bad consequences caused by low reactivity or resistance, this make of nitrate in the emergency department accepts angina patients drug resistance quickly identify the more important ^[9].

4. Clinical management strategies for nitrate resistance

According to the current guidelines for the application of nitrates, there is no consistent and effective treatment for resistance to nitrates at present, and it is important to identify and prevent it early. Timely identification of nitrate resistance, especially in patients with acute cardiac events who do not respond to GTN, has important clinical value. Once the patients with no response or low response are found, integrated traditional Chinese and Western medicine treatment should be paid attention to ^[10].

4.1. Improvement of drug use

In general, intermittent administration, eccentric administration, gradual increase, and combination therapy can be used to prevent the occurrence of nitrate resistance.

4.1.1. Intermittent administration method

According to the half-life of nitrate drugs, it is necessary to ensure that there is a certain nitrate-free period every day so that endothelial cells and smooth muscle cells can resume the response to nitrate ^[11]. (Nitroglycerin should be more than 8–12 hours, indomethacin should be more than 12–14 hours).

4.1.2. Eccentric administration method

Oral administration can be taken at 8 am and 2 pm, medication time in the first 8 hours of 24 hours, not after 16 hours ^[12]. Therefore, the concentration decreases in the last 8 hours, resulting in an 8-hour nitrate-free interval. “If the drug is administered intravenously, it should not be administered continuously for 24 hours, but only for 15 to 16 hours to ensure that the endothelial and smooth muscle cells can resume their response to nitrate.” If the membrane is applied, the membrane is applied for 16 hours, and the membrane needs to be removed after 8 hours, that is, an 8-hour nitrate-free interval is produced. In addition, there is no time limit when the drug is given by mouth or spray, and it can be used normally ^[13].

4.1.3. Incremental method

For patients with severe unstable angina pectoris, when the drug concentration in the body drops to the lowest level in the late night or early morning when using intermittent or eccentric dosing methods, angina pectoris is prone to occur. This phenomenon is called the “zero point phenomenon” or “rebound phenomenon.” To avoid this phenomenon, a gradual incremental method can be used, such as giving 5 mg, 10 mg, and 15 mg of analgesia in the early, middle, and late, respectively, and adding a dose of non-nitrate vasodilator drugs (such as β -blockers or Ca^{2+} channel blockers) before bed, which can avoid both nitrate resistance and the occurrence of the zero-point phenomenon. If angina pectoris occurs during this period, sublingual administration of nitroglycerin can be used to relieve symptoms^[14-15].

4.1.4. Combination therapy

(1) Angiotensin II converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB)

According to the neurohormone activation theory, continuous use of nitrates within 48 hours can lead to the activation of RASS due to the baroreceptor effect, and the secretion of angiotensin II (AngII) and angiotensin II receptor 1 (AT1) increases, which makes the blood vessels more sensitive to a variety of vasoconstrictor substances such as AngII and reduces the vasodilator effect of nitroglycerin. Clinical studies have also shown that ACEI and ARB can reduce the incidence of nitrate resistance in patients with coronary heart disease. Therefore, ACEI or ARB can reduce the sensitivity of blood vessels to vasoconstrictors when using nitroglycerin, which is beneficial in preventing nitroglycerin resistance^[16].

(2) Sulfhydryl donor

Several animal experiments have confirmed that nitroglycerin metabolism requires sulfhydryl to produce NO. Continuous use of nitroglycerin leads to the gradual consumption of vascular sulfhydryl groups and the reduction of NO secretion. For example, N-acetylcysteine can enhance its effect by directly non-enzymatic binding to GTN, which is beneficial to restore ALDH2 activity and prevent nitrate resistance. Therefore, the addition of sulfhydryl donor drugs such as N-acetylcysteine, methionine and captopril to nitroglycerin can prevent and reverse the resistance to nitroglycerin^[17].

(3) Folic acid

Studies have found that the dysfunction of nitric oxide synthase (NOS) is related to the excessive production of superoxide anion, which may be related to the decreased activity of tetrahydrobiopterin, a cofactor of NOS. Tetrahydrobiopterin supplementation has been shown to reverse the dysfunction of NOS in the high oxidation state caused by continuous use of nitroglycerin, etc. Folic acid is beneficial to the recovery of tetrahydrobiopterin activity. Folic acid supplementation can reverse endothelial dysfunction by regulating tetrahydrobiopterin metabolism and restoring nitric oxide synthase metabolism.

(4) Other pharmacologic diuretics

The mechanism of pseudoresistance to nitrate may be related to the counter regulation effect of RASS activation and the increase of vascular volume. Diuretics can alleviate pseudoresistance by reducing water and sodium retention.

(5) Statins

Atorvastatin can enhance the effect of NO by reducing the generation of oxygen ions in vascular tissue. It can also reduce the production of O^{2-} in endothelial cells by reducing the level of serum low-density lipoprotein cholesterol (LDL-C) and preventing the P21rac isoprenylation pathway to inhibit the activation of NADPH membrane oxidase, thereby reducing the resistance to nitrate drugs.

(6) Vasodilators

Hydralazine can reduce the sensitivity of vascular endothelial cells to vasoconstrictor drugs, thereby

reducing the resistance to nitrates.

(7) Antioxidative drugs

Previous studies have shown that vitamin C, E, coenzyme Q10, and probucol can remove superoxide anion and reduce NO inactivation, and their combined application can maintain the sensitivity of blood vessels to nitroglycerin. L-arginine, folic acid and their derivatives can prevent the uncoupling of eNOS and the increase of superoxide anion and can avoid nitrate resistance. Exogenous methionine or zinc chloride, which induces the production of endogenous methionine, can also prevent the development of nitrate resistance. Carvedilol can not only inhibit sympathetic nerve activity, but also has antioxidant and free radical scavenging effects, and has the preventive effect of nitroglycerin resistance^[18].

4.1.5. Other stable angina pectoris

They can be used for physical activity before the temporary preventive use of nitrate, or the presence of chest tightness in the premonitory use of sublingual medication, usually do not use nitrate drugs, to avoid drug resistance. For temporary medication caused by emergencies, short-acting and fast-acting drugs should be selected as far as possible, such as nitroglycerin or isosorbide dinitrate. After taking effect, the blood drug concentration can decrease rapidly, and it is not easy to produce drug resistance .

4.2. Traditional Chinese Medicine therapy

- (1) Commonly used drugs for acute onset of chest pain: Suxiao Jiuxin pill, Shexiang Baixin pill, Kuanchest aerosol, Guanxin Suhe pill, etc.
- (2) Commonly used drugs in remission period: Suxiao Jiuxin pill, Fufang Salvia, Suhexiang pill, Qili Qiangxin capsule and other preparations^[19].
- (3) The main clinical manifestations are shock caused by hypovolemia, decreased blood pressure and decreased heart rate. In this clinical situation, nitrates are relatively contraindicated, and Chinese patent medicine such as Shenmai injection, Shenfu injection, etc.^[20]
- (4) Oral agents such as Qishen Yiqi pills, Tongmai Yangxin pills, Xinbao pills, etc.

5. Summary

Despite the rapid development of medicine in the past century, nitrates are still the most commonly used drugs for the treatment of acute and critical diseases such as angina pectoris, myocardial ischemia, acute heart failure, and hypertension. However, drug resistance to nitrates is also common, and its resistance mechanism has not been fully elucidated. At present, there is no unified treatment plan for drug resistance, and early and rapid identification and prevention are the most important. A comprehensive understanding of the clinical management strategy of nitrate resistance will greatly benefit the reduction of clinical adverse events and the improvement of patient treatment.

Disclosure statement

The authors declare no conflict of interest.

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The Impact of Improved and Refined Education on Anxiety After Interventional Surgery for Cerebrovascular Disease

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Abstract: *Objective:* To explore the impact of modified and refined health education on anxiety among patients undergoing interventional therapy for cerebrovascular diseases. *Methods:* Eighty patients with cerebrovascular diseases who underwent interventional therapy at the hospital from June 2023 to June 2024 were selected as the study subjects. They were divided into an observation group and a control group according to the random number table method, with 40 patients in each group. The control group received conventional health education, while the observation group received modified and refined health education. The Self-Rating Anxiety Scale (SAS) scores were compared between the two groups after the procedure. *Results:* There were no significant differences between the two groups in terms of gender, age, education level, and duration of illness ($P > 0.05$). The SAS score in the observation group was significantly lower than that in the control group, showing a highly significant correlation ($P < 0.001$). *Conclusion:* Modified and refined health education can effectively reduce anxiety levels among patients undergoing interventional therapy for cerebrovascular diseases and improve their quality of life, making it worthy of clinical promotion and application.

Keywords: Cerebrovascular disease; Endovascular interventional surgery; Modified and refined health education; Anxiety; Self-Rating Anxiety Scale (SAS)

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1. Introduction

Cerebral angiography plays a pivotal role in the diagnosis of cerebrovascular diseases and is recognized as the “gold standard”^[1-3]. However, it is important to note that this examination method is invasive and often leads to changes in patients' blood pressure and heart rate^[2]. During the interventional treatment of cerebrovascular diseases, patients are often filled with concerns. On the one hand, they worry about the possible adverse reactions of the treatment, and on the other hand, they have doubts about the clinical efficacy. Such concerns make patients prone to developing negative emotions such as tension, anxiety, and depression, which can have various negative impacts

on them ^[4]. For example, anxiety may affect patients' sleep quality, thereby affecting their physical recovery; depression may reduce patients' enthusiasm for treatment and affect the treatment outcome. Health education plays a crucial role in this process. It can effectively improve patients' cognitive level of the disease, allowing them to better understand their condition's characteristics, treatment methods, and prognosis, thus helping them build confidence to overcome the disease ^[5]. However, traditional health education methods have certain limitations. Traditional health education often takes the form of oral explanations and distributing promotional brochures, which are generally more singular and not conducive to patients and their families' understanding and remembering the educational content. Moreover, traditional health education lacks personalization and cannot provide targeted education based on each patient's specific situation, making it difficult to achieve the desired results ^[6].

2. Materials and methods

2.1. General information

Eighty patients with cerebrovascular disease who underwent interventional therapy in the hospital from June 2023 to June 2024 were selected as the study subjects. The inclusion criteria were: (1) meeting the diagnostic criteria for cerebrovascular disease ^[7]; (2) aged between 20 and 75 years old; (3) undergoing interventional therapy for the first time; (4) signing the informed consent form.

The exclusion criteria were: (1) having severe cardiac, pulmonary, liver, kidney, or other organ dysfunction; (2) having severe mental illness; (3) being unable to complete the questionnaire survey. The patients were divided into an observation group and a control group using a random number table method, with 40 patients in each group.

2.2. Methods

Both groups of patients received interventional therapy for cerebrovascular disease, and routine preoperative education was provided, covering vital signs monitoring, neurological signs evaluation, medication guidance, etc.

2.3. Control group

Patients in the control group received routine preoperative education. The education content included disease-related knowledge, interventional surgery procedures, preoperative preparations, postoperative precautions, etc. Traditional methods such as oral explanation and distribution of promotional brochures were mainly used for implementation.

2.4. Observation group

2.4.1. Preoperative education

(1) Establish a good doctor-patient relationship

Doctors should proactively communicate with patients. Firstly, introduce themselves and the members of the interventional surgery team to allow patients to have a preliminary understanding and trust in the medical team. Then, gain a detailed understanding of the patient's condition, anxiety level, cognitive ability, learning style, and other aspects.

(2) Explain disease-related knowledge

Use illustrative educational manuals, vivid and intuitive videos, and other formats to explain the causes, pathogenesis, and hazards of cerebrovascular diseases, as well as the principles, advantages, and risks of interventional therapy, in an easy-to-understand manner.

(3) Introduce the interventional surgery process and precautions

Provide patients with a detailed explanation of the interventional surgery process, including preoperative

preparations such as clarifying the fasting time for food and water, skin preparation, and drug sensitivity tests. Inform them about possible experiences during the surgery, such as the level of pain during puncture and discomfort during contrast agent injection. Also, advise on postoperative precautions such as bed rest time, care methods for the puncture site, and dietary guidance. Conduct on-site simulations and demonstrations to help patients familiarize themselves with the surgical process, enhance their confidence in the surgery, and reduce their concerns and fears about the procedure.

2.4.2. Intraoperative education

- (1) Maintain a comfortable operating room environment
Strive to create a quiet, clean, and temperature-appropriate operating room environment. Playing soothing music can help alleviate patients' anxiety and allow them to undergo surgery in a relatively relaxed state.
- (2) Strengthen communication with patients
During the surgical procedure, doctors should closely monitor patients' emotional changes. Timely verbal communication with patients is essential to encourage their active cooperation during the surgery.

2.4.3. Postoperative education

- (1) Focus on patients' psychological changes
In the early postoperative period, medical staff should exert great importance on patients' psychological states. Promptly identify patients' anxiety and provide targeted psychological counseling. This helps patients relieve postoperative psychological stress and promotes their psychological recovery.
- (2) Guide patients in functional exercise
Develop personalized functional exercise plans based on the patient's specific conditions and physical status. Provide on-site guidance and supervision to ensure patients perform functional exercises correctly. This aids in the early recovery of patients' limb function and improves their quality of life.
- (3) Provide discharge guidance
Educate patients on the relevant knowledge of secondary prevention of cerebrovascular diseases. This includes the importance of a balanced diet, methods of moderate exercise, the benefits of regular sleep schedules, the necessity of smoking cessation and alcohol restriction, and the significance of controlling blood pressure, blood sugar, and blood lipids. Guide patients to take medications regularly and undergo periodic check-ups to prevent the recurrence of cerebrovascular diseases.

2.5. Observation indicators

The Self-Rating Anxiety Scale (SAS) was employed to evaluate the anxiety levels of patients in both groups. This scale consists of 20 items, rated on a 4-point scale where 1 to 4 represent "none or a little of the time," "some of the time," "a good part of the time," and "most or all of the time," respectively. Higher scores indicate more severe anxiety. A SAS total score of 50 or above is considered indicative of anxiety symptoms, with 50–59 being mild anxiety, 60–69 moderate anxiety, and 70 or above severe anxiety. Both groups of patients completed the SAS on the day before surgery and on the 7th day after surgery.

2.6. Statistical methods

Statistical analysis was performed using SPSS 27.0 software. Measurement data conforming to a normal distribution were expressed as mean \pm standard deviation (SD), and comparisons between the two groups were made using the *t*-test. Count data were expressed as the number of cases (*n*) and percentage (%), and comparisons between the two groups were conducted using the χ^2 test. A *P*-value less than 0.05 was considered statistically significant.

3. Results

3.1. Comparison of general information between the two groups

There were no statistically significant differences between the two groups in terms of gender, age, education level, and course of disease ($P > 0.05$), making them non-comparable (Table 1).

Table 1. Comparison of general information between the two groups

Group	Number of Cases (n)	Gender (n)	Average age (\pm s, years)	Average course of disease (\pm s, months)	Education level (n)	Men	Women	Junior high school and below	High school	University and above
Control group	40	20	20	58.35 \pm 11.72	6.23 \pm 1.17	15	12	13		
Observation group	40	18	22	56.21 \pm 11.18	5.85 \pm 1.98	17	11	12		
χ^2/t value		0.201	0.836	1.045	0.209					
p value		0.654	0.406	0.299	0.901					

3.2. Comparison of SAS scores between the two groups

The SAS scores of the observation group were significantly lower than those of the control group, showing a highly significant correlation ($P < 0.001$) (Table 2).

Table 2. Comparison of SAS scores between the two groups (\pm s, scores)

Group	Number of cases (n)	SAS score
Control group	40	57.65 \pm 16.77
Observation group	40	38.26 \pm 15.85
t -value		5.315
p -value		< 0.001

4. Conclusion

Cerebrovascular disease, as a common and frequently occurring disease that seriously harms human health, brings heavy burdens to countless families due to its high incidence, high disability rate, and high mortality rate. These characteristics of cerebrovascular disease make it one of the urgent problems to be overcome in the medical field [8]. In recent years, endovascular interventional therapy has rapidly emerged as an important means of treating cerebrovascular diseases. Compared with traditional surgical procedures, endovascular interventional therapy has significant advantages, such as minimal trauma, faster patient recovery, and fewer complications. For this reason, it has gradually become the preferred method for treating cerebrovascular diseases [9]. However, despite its many advantages, cerebrovascular interventional therapy is also a complex technique. Patients face multiple stresses during the perioperative period, including physical pain and psychological burden caused by the disease itself, as well as surgical trauma and unfamiliar hospital environments. Under the influence of these stresses, patients are prone to develop negative emotions such as anxiety, depression, and fear. These negative emotions not only affect their treatment compliance, making it difficult for patients to actively cooperate with treatment but also have adverse effects on the prognosis of the disease [10]. Therefore, how to effectively alleviate the anxiety of patients after cerebrovascular interventional surgery, and thereby improve their prognosis, has become an important topic in clinical nursing work.

This study suggests that the SAS scores of patients in the observation group were significantly lower than those in the control group ($P < 0.05$), fully indicating that improved and refined education can effectively reduce the anxiety level of patients after cerebrovascular interventional surgery. An in-depth analysis of the reasons may be related to the following factors. On the one hand, according to relevant principles in the medical field, when patients are in a state of tension and anxiety, the excitability of the sympathetic nerves inside the human body will significantly increase^[11]. Under the effect of this physiological change, the content of substances with vasoconstrictive properties, such as catecholamines, in the blood will increase accordingly. The increase in the content of such substances will inevitably trigger a series of chained physical reactions, specifically manifested as a significant acceleration in the patient's heart rate and a synchronous increase in blood pressure. As a result, it greatly increases the chance of surgical complications, which can have a non-negligible negative effect on the smooth progress of interventional therapy and the prognosis of patients after surgery^[11]. On the other hand, it has been reported that there is a very close and direct correlation between the final effect of cerebrovascular interventional therapy and the quality of nursing care implemented^[12,13]. This fully illustrates the importance of quality and appropriate educational nursing for the effectiveness of cerebrovascular interventional therapy. In addition, the research results of many scholars also provide strong evidence for the above viewpoint from different perspectives. For example, Li *et al.* (2019) clearly stated in their related research that when psychological nursing is implemented for patients undergoing cerebrovascular interventional therapy, it can significantly reduce adverse emotions such as anxiety and depression generated by patients, and at the same time, it can also effectively reduce the probability of complications^[14]. Furthermore, in Yang (2017) on patients undergoing cerebrovascular interventional surgery, targeted nursing measures were taken^[15]. Specifically, patients were provided with extremely adequate educational work on interventional knowledge in the preoperative stage, enabling patients to have a comprehensive and in-depth understanding of their illness. After such treatment, the patient's anxiety has been significantly improved, and the incidence of complications has also shown a significant decrease after surgery.

In summary, improved and refined education is a safe and effective nursing intervention measure. It effectively alleviates the anxiety level of patients after cerebrovascular interventional surgery and improves the quality of life of patients by establishing a good nurse-patient relationship, providing comprehensive and diverse educational content, and focusing on psychological support. It is worthy of wide application in clinical practice. It is believed that the continuous in-depth research and application of improved and refined education, will bring good news to more patients with cerebrovascular disease, helping them better overcome the disease and return to normal life.

Disclosure statement

The authors declare no conflict of interest.

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Research Progress of Astragaloside IV in the Treatment of Cardiovascular Diseases

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Abstract: Cardiovascular disease (CVD) continues to dominate as the primary cause of mortality and morbidity worldwide, constituting a pressing global health concern. In contrast to Western medicine, traditional Chinese medicine (TCM) offers a holistic, side-effect-minimizing, and highly efficacious approach to tackling CVD challenges. Among the myriad herbs utilized in TCM, Huangqi (HQ), particularly in the realm of cardiovascular therapeutics, has enjoyed an esteemed status spanning millennia. Astragaloside IV (AS-IV), a saponin derivative meticulously extracted from the roots of the renowned Chinese medicinal plant *Astragalus membranaceus*, has garnered significant attention for its multifaceted cardioprotective capabilities. These encompass antioxidant stress mitigation, anti-inflammatory actions, anti-apoptotic effects, inhibition of cardiomyocyte hypertrophy, and attenuation of myocardial fibrosis, among others. Consequently, pharmacokinetic and toxicological evaluations underscore AS-IV's low bioavailability yet commendable safety profile, with a notable caveat of prudence when administering to pregnant individuals. The present article delves into the most recent advancements in understanding the therapeutic impacts and underlying mechanisms of AS-IV in the context of cardiovascular diseases. By consolidating these cutting-edge findings, we aspire to establish a robust theoretical foundation that can propel the development of AS-IV as an innovative therapeutic agent for the treatment of CVDs, thereby contributing to the global endeavor to combat this pervasive health burden.

Keywords: Astragaloside IV; Cardiovascular diseases; Pharmacology

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1. Introduction

Cardiovascular disease (CVD) stands as the foremost contributor to mortality in China's population health, earning it the sobriquet of the "number one killer." Annually, approximately one million lives are lost to CVD, constituting roughly 45% of the country's total mortality rate, posing a dire threat to human wellbeing. Amidst this escalating burden of CVD, relentless efforts have been directed toward discovering novel drugs and therapeutic strategies. Undeniably, CVD has transformed into a pressing public health crisis. The groundbreaking discovery of artemisinin by Tu Youyou underscores the immense potential harbored within traditional Chinese medicine (TCM).

Over the past few decades, natural compounds derived from Chinese herbal medicines have emerged as invaluable resources for drug research and development, particularly in the realm of CVD treatment. These compounds offer promising avenues for addressing the challenges posed by CVD and represent a significant advancement in the quest for innovative therapeutic solutions^[1].

Astragaloside IV (AS-IV), a pivotal constituent extracted from *Astragalus membranaceus* var *mongholicus* (commonly known as Huangqi, HQ, in China), boasts a rich history as a fundamental Qi-tonifying medicine renowned for its broad therapeutic spectrum. Frequently employed in the prevention and management of heart diseases^[2]. HQ is characterized by its gentle yet potent actions, diverse therapeutic targets, minimal toxic side effects, cost-effectiveness, and overall safety. Its chemical makeup encompasses a diverse array of glycosides, polysaccharides, amino acids, and trace elements, collectively contributing to its status as a natural antioxidant. Notably, HQ’s therapeutic prowess stems from three primary ingredients: HQ saponins, HQ polysaccharides, and HQ flavonoids, with AS-IV occupying a prominent position among the saponin fraction. Possessing poor water solubility yet readily soluble in ethanol, AS-IV carries a molecular formula of C₄₁H₆₈O₁₄ and a molecular weight of 784.98. Its medicinal scope extends across multiple physiological systems, encompassing the digestive, nervous, endocrine, respiratory, urinary, hematological, and cardiovascular systems. Within the realm of cardiovascular medicine, AS-IV has garnered extensive research attention, particularly in the treatment of cardiovascular diseases (CVDs), yielding notable advancements that pave the way for novel drug development. This article comprehensively summarizes the cardiovascular pharmacological activities of AS-IV, delving into its therapeutic effects and underlying mechanisms in addressing CVDs. By consolidating the latest findings, the study aims to provide a comprehensive overview of AS-IV’s potential as a therapeutic agent, fostering further exploration and innovation in the field of cardiovascular therapeutics.

AS-IV, a naturally occurring compound meticulously extracted and purified from the medicinal herb *Astragalus membranaceus*, exhibits a versatile array of pharmacological properties, including potent anti-inflammatory^[3], antioxidant^[4], anti-myocardial hypertrophic^[5], anti-myocardial apoptotic^[6], and anti-myocardial fibrotic activities^[7] (**Figure 1**). Its burgeoning application in the cardiovascular domain is steadily yielding groundbreaking advancements. Despite these promising prospects, the current research landscape surrounding AS-IV remains relatively circumscribed. To gain a deeper insight into the progress made in elucidating AS-IV’s therapeutic potential for cardiovascular diseases (CVDs), we embarked on a comprehensive review of the systematic studies conducted on AS-IV in recent years. This endeavor aimed to provide a consolidated and up-to-date summary of the research advancements, thereby facilitating further exploration and advancing the field of cardiovascular therapeutics.

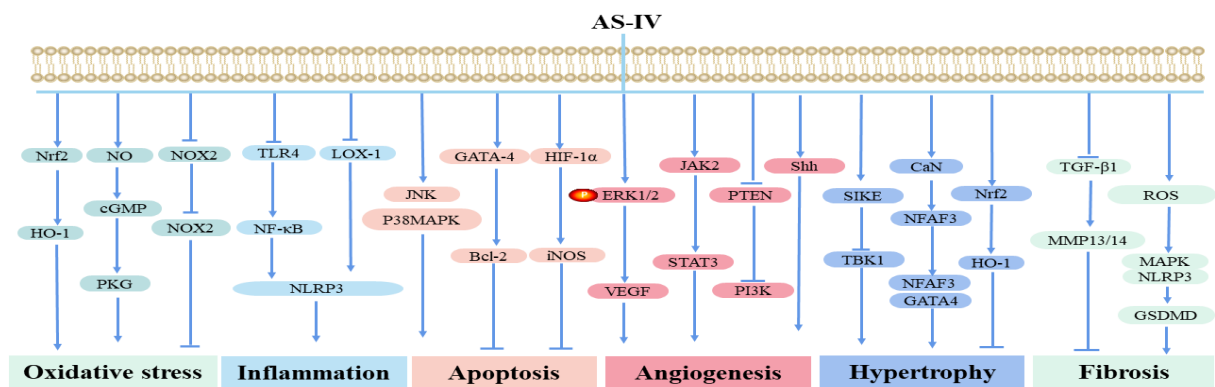


Figure 1. Pharmacological effects of AS-IV on myocardium. AS-IV has protective effects such as anti-cardiomyocyte hypertrophy, anti-fibrosis, antioxidant stress, anti-inflammatory, anti-apoptosis, and promotion of angiogenesis.

2. Chemical structure and pharmacological properties of AS-IV

Astragaloside IV (CHEBI: 65457 Astragaloside IV) (chemical structure presented in **Figure 2**) is a pentacyclic triterpenoid that is cycloastragenol having beta-D-xylopyranosyl and beta-D-glucopyranosyl residues attached at positions O-3 and O-6 respectively. It has a role as an EC 4.2.1.1 (carbonic anhydrase) inhibitor, an anti-inflammatory agent, a neuroprotective agent, an antioxidant, a pro-angiogenic agent and a plant metabolite. It is a triterpenoid saponin and a pentacyclic triterpenoid. It is functionally related to a cycloastragenol. The detailed physicochemical properties of AS-IV are summarized in **Table 1**.

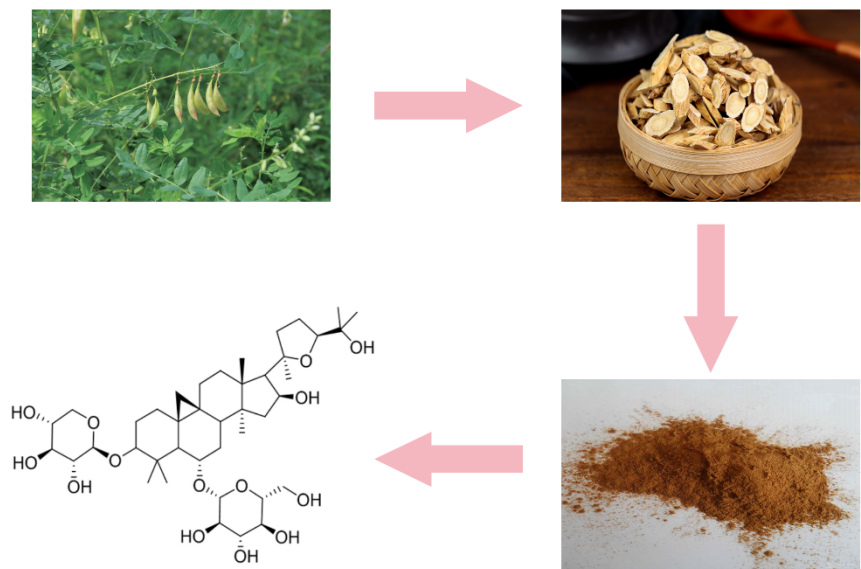


Figure 2. Structure and origin of AS-IV. AS-IV is a pentacyclic triterpenoid that is cycloastragenol having β -D-xylopyranosyl and β -D-glucopyranosyl residues attached at positions O-3 and O-6 respectively. The detailed physicochemical properties of AS-IV was sourced from CHEBI.

Table 1. Physicochemical properties of Astragaloside IV

Content	Description
Name	Astragaloside IV
Molecular formula	$C_{41}H_{68}O_{14}$
Another name in English	(3 β ,6 α ,9 β ,16 β ,20R,24S)-16,25-Dihydroxy-3-(β -D-xylopyranosyloxy)-20,24-epoxy-9,19-cyclolanostan-6-yl β -D-glucopyranoside
Molecular weight	785.0 g/mol
PSA	228.22000
LogP	1.96
Boiling point	895.7 \pm 65.0 $^{\circ}$ C at 760 mmHg
Melting point	295–296 $^{\circ}$ C
Appearance traits	White crystalline powder
Molecular weight	784.970 g/mol
Flash point	495.5 \pm 34.3 $^{\circ}$ C
Refractive index	1.621
Storage conditions	2–8 $^{\circ}$ C
Density	1.4 \pm 0.1 g/cm ³

3. Potential pharmacological effects of Astragaloside IV on cardiovascular diseases

3.1. Inhibit oxidative stress

Oxidative stress represents an intricate imbalance within the physiological milieu, characterized by a heightened presence of oxidants and a concurrent decline in antioxidants. This state is particularly marked by the pivotal role of reactive oxygen species (ROS), whose excessive generation, when coupled with nitric oxide (NO) to yield peroxynitrite, diminishes NO's biological efficacy and precipitates endothelial dysfunction. Myocardial ischemia/reperfusion (I/R) injury poses a formidable clinical challenge, as the initial moments of reperfusion following ischemia precipitate a surge of free radicals, which, coupled with reduced antioxidant defenses, renders the myocardium acutely susceptible to damage^[8]. Succinic acid, a vital intermediate in the tricarboxylic acid (TCA) cycle, has been implicated in the amplification of ROS production during I/R processes^[9]. Notably, Jiang *et al.* (2019) demonstrated that AS-IV, administered at a dose of 40 mg/kg, effectively mitigated the accumulation of succinic acid in the myocardium of Sprague-Dawley (SD) rats subjected to I/R, subsequently attenuating ROS generation. Furthermore, AS-IV activates the Nrf2/HO-1 signaling cascade, upregulating the expression of antioxidant enzymes, thereby conferring a cardioprotective benefit^[10]. Glycogen synthase kinase-3 β (GSK-3 β) emerges as a central regulator in the orchestration of cellular apoptosis^[11]. In this context, He *et al.* (2012) revealed that AS-IV, at a concentration of 50 μ M, inhibits oxidative stress-mediated mitochondrial permeability transition pore (mPTP) opening in H9C2 cells through the NO/cGMP/PKG/GSK-3 β signaling pathway^[12]. Additionally, AS-IV, administered at doses of 5 and 10 mg/kg, mitigated myocardial I/R injury in SD rats by modulating the PI3K/Akt pathway, leading to GSK-3 β phosphorylation, further underscoring its cardioprotective potential^[13].

Doxorubicin (DOX), a cornerstone of anti-tumor chemotherapy, is notorious for its potential to inflict severe cardiac toxicity. This toxicity is underpinned by DOX's ability to elicit oxidative stress, a process facilitated by the upregulation of NADPH oxidase isoforms NOX2 and NOX4 in rat hearts, ultimately culminating in cardiomyopathy^[14]. Lin *et al.* (2019) seminally reported that AS-IV, administered at a dose of 40 mg/kg, effectively mitigated myocardial injury, apoptosis, fibrosis, and dysfunction in C57BL/6 mice exposed to DOX, achieving this by suppressing the expression of NOX2 and NOX4^[15]. Furthermore, AS-IV has been shown to bolster the myocardial antioxidant defense system, as evidenced by its enhancement of superoxide dismutase (SOD), glutathione peroxidase (GSH-PX), and catalase (CAT) activities in both mouse models of viral myocarditis and rat models of DOX-induced heart injury. Concurrently, AS-IV reduced the levels of myeloperoxidase (MPO) and reactive oxygen species (ROS), thereby alleviating oxidative stress^[15,16]. Calpain-1, a protease present in endothelial cells, has been implicated in the pathogenesis of endothelial dysfunction^[17]. Nie *et al.* (2019) interestingly discovered that AS-IV could ameliorate endothelial dysfunction in the thoracic aorta of diabetic rats by dual mechanisms, decreasing oxidative stress and inhibiting Calpain-1 activity^[18]. This finding underscores the multifaceted cardioprotective effects of AS-IV and highlights its potential as a therapeutic strategy for mitigating the adverse cardiac effects of DOX and other oxidative stress-mediated conditions.

3.2. Anti-inflammatory

Inflammation stands as a pivotal and independent cardiovascular risk factor, with the capacity to not only inflict endothelial damage but also contribute significantly to the pathogenesis of endothelial dysfunction^[19]. In the inflammatory cascade, cellular inflammatory factors adhere to and aggregate on endothelial cells, triggering the release of noxious metabolites from vascular endothelial cells. This process disrupts the structural and functional integrity of the endothelium, thereby precipitating endothelial dysfunction^[20]. By understanding these intricate mechanisms, more insights can be gained into the role of inflammation in cardiovascular health and devise strategies to mitigate its adverse effects.

AS-IV glycoside exerts its anti-inflammatory effects by disrupting the inflammatory signaling pathway,

thereby mitigating the deleterious impact of the inflammatory response on endothelial cells. The expression of adhesion molecules, notably vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), on the endothelial cell surface plays a pivotal role in the initiation and progression of inflammation. In the presence of inflammation, these adhesion molecules facilitate the adherence of white blood cells to endothelial cells ^[21]. Notably, the TLR4/NF- κ B signaling pathway regulates the expression of VCAM-1 and ICAM-1, underscoring its importance in the inflammatory process ^[22]. AS-IV demonstrates efficacy in ameliorating vascular endothelial dysfunction associated with hyperglycemia. It achieves this by reducing elevated levels of interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), while concurrently decreasing the expression of VCAM-1 and ICAM-1 ^[23]. The protective effects of AS-IV may be mediated, at least in part, through the TLR4/NF- κ B signaling pathway. In the context of diabetic angiopathy, the accumulation of oxidized low-density lipoprotein (ox-LDL) exacerbates endothelial cell injury through a multifaceted mechanism involving increased oxidative stress, augmented inflammatory response, and heightened secretion of adhesion molecules ^[24]. Ox-LDL triggers inflammation by stimulating the production of numerous inflammatory cytokines, including IL- β , whose maturation is orchestrated by the NLRP3 inflammasome. Additionally, ox-LDL activates the NLRP3 inflammasome, leading to the secretion of IL-1 β in macrophages ^[25]. Remarkably, AS-IV safeguards endothelial progenitor cells (EPCs) from oxLDL-induced dysfunction by targeting the LOX-1/NLRP3 signaling pathway ^[26].

Toll-like receptor 4 (TLR4) stands as a pivotal LPS receptor and a crucial mediator of proinflammatory responses. Zhang *et al.* (2019) have demonstrated that AS-IV, administered at doses of 20, 40, and 80 mg/kg, significantly ameliorated heart function, myocardial cell viability, and pathological alterations elicited by lipopolysaccharide (LPS) exposure in C57BL/6J mice. Furthermore, AS-IV effectively reduced the concentrations of interleukin-1 β (IL-1 β), IL-6, and tumor necrosis factor- α (TNF- α) within myocardial tissue ^[27]. In a separate study, Yang *et al.* (2013) induced a myocardial hypertrophy model through intraperitoneal injections of isoproterenol (5 mg/kg/d) and observed that AS-IV, at doses of 20, 40, and 80 mg/kg, inhibited myocardial hypertrophy and reduced serum levels of TNF- α and IL-6. Their findings suggested that this protective effect was associated with the inhibition of the TLR4/NF- κ B signaling pathway ^[28]. Shi *et al.* (2021) further elaborated on the therapeutic potential of AS-IV in myocardial inflammation, reporting that AS-IV (80 mg/kg/day) alleviated myocarditis in SD rats with acute myocardial infarction (AMI) by suppressing the TLR4/MyD88/NF- κ B pathway ^[29]. Extending the investigation to sepsis-induced cardiac dysfunction, Huang *et al.* (2021) examined the effects of AS-IV on rats subjected to cecal ligation and puncture (CLP). They found that AS-IV (40 mg/kg/d) mitigated myocardial cell apoptosis post-CLP surgery and reduced serum levels of inflammatory markers, including IL-6, IL-10, and high mobility group box 1 (HMGB-1) ^[30]. Collectively, these studies underscore the multifaceted protective roles of AS-IV in mitigating cardiac dysfunction and inflammation, particularly through its modulation of the TLR4/NF- κ B signaling pathway and its downstream inflammatory cascades.

3.3. Anti-myocardial apoptosis

Apoptosis holds a pivotal role in numerous tissue cell types, and its regulation is orchestrated by a complex network of genes. Notably, the *Bcl-2* gene family, which was the first to be identified as a key regulator of apoptosis, comprises members such as *Bcl-2*, *Bax*, *Bcl-XS*, and *Bcl-XL*, with some promoting while others inhibiting apoptosis ^[31]. Prior research has established that the delicate balance of *Bcl-2/Bax* expression ratios in cardiac myocytes during both physiological and pathological processes dictates cell fate, either fostering survival or inducing death ^[32]. Furthermore, evidence suggests that AS-IV exerts a protective effect in myocardial injury scenarios, specifically by downregulating *Bax* expression and upregulating *Bcl-2* expression. This modulation results in an elevated *Bcl-2/Bax* ratio, ultimately inhibiting myocardial cell apoptosis and mitigating myocardial

damage following doxorubicin-induced injury^[33]. In an experimental model involving intraperitoneal inoculation of Coxsackievirus B3 in *Balb/c* mice, AS-IV significantly reduced the apoptosis index of compromised myocardial cells, thereby showcasing its potent anti-apoptotic properties. This finding further underscores AS-IV's ability to indirectly delay or even reverse myocardial fibrosis^[34]. The apoptosis of myocardial cells is intricately tied to the expression of apoptotic genes. AS-IV's therapeutic mechanism involves inhibiting the expression of various genes that promote myocardial cell apoptosis, thereby suppressing cell death and preserving cardiac function.

The MAPK signaling cascade plays a crucial role in modulating cell apoptosis, encompassing three distinct kinase families: c-Jun N-terminal kinases (JNKs), extracellular signal-regulated kinases (ERKs), and p38 mitogen-activated protein kinases (p38 MAPKs)^[35,36]. Sun *et al.* (2021) demonstrated that AS-IV, at concentrations of 10 or 50 ng/mL, effectively safeguards H9C2 cells against apoptosis triggered by high glucose/high fat (HG/HF) conditions and hypoxia. This protective effect is attributed to its ability to dampen the activation of JNK and p38 signaling pathways while fostering the activation of the ERK signaling pathway^[37]. In animal studies, AS-IV administration at doses of 10 and 50 mg/kg/day to C57BL/6 mice mitigated cardiac dysfunction induced by streptozotocin (STZ) through fine-tuning the MAPK signaling pathway. This intervention not only inhibited myocardial fibrosis and inflammation but also preserved cardiac function^[37]. Calpain-1, a member of the cysteine protease family, has been implicated in promoting cell apoptosis during myocardial ischemia/reperfusion (I/R) and pressure/overload conditions^[38,39]. Mei *et al.* (2015) reported that AS-IV, administered at 80 mg/kg/day, attenuated isoproterenol-induced apoptosis in hypertrophic cardiomyocytes of Sprague-Dawley (SD) rats by inhibiting calpain-1 activity and mitigating oxidative stress^[40]. Moreover, Yang *et al.* (2020) observed that AS-IV, within a concentration range of 0.5–300 µg/mL, promoted *Bcl-2* expression in H9c2 cells by stimulating the overexpression of GATA-4. This upregulation led to a reduction in apoptosis induced by hypoxia/reoxygenation (H/R)^[41]. Hypoxia-inducible factor-1α (HIF-1α) serves as a pivotal regulator in the molecular response to hypoxia, enhancing oxygen transport and facilitating metabolic adaptation to hypoxic conditions through the activation of genes related to energy metabolism, angiogenesis, and cell apoptosis^[42]. Si *et al.* (2014) discovered that AS-IV, at a concentration of 50 µM, upregulated the HIF-1α/iNOS signaling pathway in rat neonatal cardiomyocytes (RNCM), leading to increased cell viability post-ischemia. This effect was accompanied by a decrease in the apoptosis index and lactate dehydrogenase (LDH) release, indicating reduced cellular damage^[43].

3.4. Promote angiogenesis

Angiogenesis, a pivotal pathological event in a myriad of chronic ischemic diseases, necessitates strategic reconstruction within ischemic regions as a paramount approach to enhancing disease prognosis^[44]. Endothelial cells, the cornerstone of vascular endothelium, are instrumental in orchestrating angiogenesis, extending from the heart to the finest microvasculature. Vascular endothelial growth factor (VEGF), a crucial regulator, propels blood vessel formation. Studies have illuminated that AS-IV fosters angiogenesis through elevating VEGF and basic fibroblast growth factor (bFGF) levels. Wang *et al.* (2015) solidified this notion by demonstrating that AS-IV augments human umbilical vein endothelial cell (HUVEC) proliferation and angiogenesis via the ERK1/2 pathway activation, thereby modulating VEGF production^[45]. Notably, ERK1/2 occupies a pivotal position in the angiogenesis cascade^[46]. Furthermore, their investigation revealed that AS-IV, at concentrations of 10, 40, and 120 µM, accentuates HUVEC proliferation, migration, and tubular formation mechanisms by upregulating ERK1/2 phosphorylation and engaging the JAK2/STAT3 pathway^[47]. In addition to these findings, Zhang *et al.* (2012) contributed to the understanding by uncovering that AS-IV, specifically at concentrations of 10 µg/mL and 100 µg/mL, promotes angiogenesis in HUVECs through the Akt pathway activation^[48].

Furthermore, the overexpression of phosphatase and tensin homolog (*PTEN*) deleted on chromosome ten,

a gene absent from the human chromosome, is implicated in eliciting endothelial dysfunction, a condition that predisposes thrombosis. Conversely, downregulation of *PTEN* expression fosters VEGF expression, subsequently stimulating angiogenesis via potentiation of VEGF-mediated signal transduction in target cells ^[49]. Cheng *et al.* (2019) demonstrated that AS-IV exerts a reparative effect on cardiac function post-myocardial infarction, accompanied by heightened survival rates, diminished infarct sizes, amelioration of pathological alterations and fibrosis, as well as augmented angiogenesis, thereby corroborating AS-IV's angiogenic and cardioprotective properties post-infarction. This salutary effect is mediated, in part, through the PTEN/PI3K/Akt signaling cascade ^[50]. Moreover, STAT3 occupies a pivotal position in angiogenesis within the context of cardiac pathogenesis, positioning it as a promising molecular target for angiogenesis-targeted therapeutic strategies ^[51]. Sui *et al.* (2019) revealed that AS-IV stimulates angiogenesis in SD rats subjected to left coronary artery ligation-induced heart failure via activation of the JAK-STAT3 signaling pathway ^[52]. Connexin (Cx), a family of structurally interdependent transmembrane proteins, facilitates the formation of gap junctions, essential for intercellular communication. Notably, Cx37, Cx40, and Cx43 are intimately linked to the angiogenic process ^[53–55]. Li *et al.* (2018) discovered that AS-IV at a concentration of 0.2 µg/mL enhances gap junction intercellular communication by upregulating the expression of Cx37, Cx40, and Cx43, ultimately facilitating endothelial cell angiogenesis ^[56].

Sonic hedgehog (Shh) is a crucial regulator for maintaining the integrity of the coronary vascular system and acts as a potent pro-angiogenic factor in the context of ischemic diseases. Consequently, Shh emerges as a promising therapeutic target in the management of myocardial infarction. Wang *et al.* (2017) have demonstrated that both tetramethylpyrazine (TMP) and Astragaloside IV (AS-IV), either administered individually or in combination, effectively enhance left ventricular remodeling and safeguard cardiac function in a rat model of myocardial infarction. The underlying mechanism may involve the upregulation of signaling molecules associated with the Shh pathway, thereby triggering cardiac angiogenesis, as a pivotal step in their cardioprotective effects ^[57].

3.5. Anti-myocardial hypertrophy

Myocardial hypertrophy (MH) represents the heart's compensatory response to various pathological stimuli, enabling it to maintain adequate systolic function. However, prolonged MH can culminate in myocardial ischemia, arrhythmias, heart failure, and even sudden death, thereby emerging as an independent risk factor that significantly escalates the incidence and mortality rates associated with cardiovascular diseases ^[58,59]. Utilizing a mouse model of MH induced by subcutaneous isoproterenol injection, the study observed a marked increase in heart weight index (16.4%) and left heart index (24.2%) post-injection. Notably, AS-IV administration significantly mitigated these indices, indicating its potential to inhibit isoproterenol-induced MH, particularly during the early stages of heart failure or cardiac functional compensation ^[28]. Furthermore, in a model of left ventricular hypertrophy (LVH) induced by pressure overload, AS-IV demonstrated its efficacy in reducing LV mass index, plasma angiotensin II (Ang II), and aldosterone levels, along with Ang II concentrations in myocardial tissue ^[60]. This suggests that AS-IV modulates Ang II levels in both plasma and myocardial tissue, diminishes aldosterone in plasma, downregulates *ACE* gene expression, and upregulates *AT2* gene and protein expression, thereby reversing LVH. However, it did not impact *AT1* gene expression. AS-IV's ability to inhibit the overactivation of the renin-angiotensin system in pressure overload-induced MH rats underscores a potential pathway for its LVH-reversing effects. TBK1, also known as NF-κB activated kinase, promotes NF-κB translocation, leading to inflammation ^[61]. Liu *et al.* (2014) reported that AS-IV (10 and 20 mg/kg/day) attenuated MH, inflammatory responses, and cardiomyocyte apoptosis induced by aortic valve stenosis in C57BL6 mice. This was likely mediated through SIKE upregulation and inhibition of TBK1/PI3K/Akt activity. Additionally, CaN, a calcium-activated serine/threonine protein phosphatase, interacts with NFAT-3 transcription factors, facilitating their nuclear translocation

and complex formation with GATA-4, contributing to MH ^[62]. The transcription factor Nrf2, a key regulator of cellular antioxidant defenses, was found to be upregulated by AS-IV (40 and 80 mg/kg/day) in AAC-induced rat MH models, implicating the Nrf2/HO-1 signaling pathway in its mechanism of action ^[63]. *In vitro* studies using neonatal rat cardiomyocytes pretreated with AS-IV (30 μ mol/L) effectively countered MH-related total protein volume increases and ANP gene expression, underscoring its protective role ^[64]. Moreover, AS-IV inhibited ISO-mediated I κ B α degradation, thereby blocking TLR4/NF- κ B signaling activation and suppressing MH progression. These findings collectively highlight AS-IV's multifaceted mechanisms in mitigating MH, encompassing regulation of the renin-angiotensin system, inflammatory pathways, and antioxidant defenses.

3.6. Anti myocardial fibrosis

Under pathological circumstances, such as inflammation and oxidative stress, cardiac fibroblasts (CFs) undergo differentiation into myofibroblasts, concurrently leading to excessive accumulation of extracellular matrix (ECM) ^[65]. Myocardial fibrosis (MF), characterized by the disproportionate deposition of collagen fibers within the myocardium, represents a pivotal pathological hallmark in the progression of heart failure. This phenomenon directly impairs myocardial compliance and diminishes systolic function, potentially precipitating arrhythmias, exacerbating cardiac pump failure, and even culminating in sudden cardiac death. Matrix metalloproteinases (MMPs), the primary enzymatic system responsible for ECM degradation, are counterbalanced by their endogenous inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). Intriguingly, a study investigating mice with chronic myocarditis and MF revealed a substantial reduction in heart failure incidence and mortality rates among those treated with astragalus saponins. Further research underscores that astragalus saponins exert their beneficial effects by attenuating the expression of transforming growth factor- β 1 (TGF- β 1) while enhancing the expression of MMP-13 and MMP-14, thereby mitigating myocardial fibrosis in chronic myocarditis models ^[63]. This suggests that astragalus saponins' anti-fibrotic effects may stem from inhibiting TGF- β 1 signaling and upregulating MMP activity in myocardial tissue. Moreover, *in vivo* studies demonstrate that Astragaloside IV (AS-IV) protects myocardial function and tissue integrity in rats subjected to high-dose isoproterenol (Iso)-induced myocardial hypertrophy, achieved through intraperitoneal injection of 5 mg/kg/day Iso ^[66]. Notably, oxidative stress is intimately linked to myocardial fibrosis, and Dai *et al.* (2017) discovered that AS-IV (100 μ M) mitigates Iso-induced cardiac fibrosis by suppressing reactive oxygen species (ROS)-mediated MAPK activation ^[67]. Inflammation is another pivotal player in the progression of cardiac fibrosis ^[68]. The NLRP3 inflammasome, a critical regulator of inflammatory responses, promotes the maturation and release of pro-inflammatory cytokines like IL-18 and IL-1 β ^[69]. Wan *et al.* (2018) reported that AS-IV (200 mg/kg/day) alleviates Iso-induced cardiac fibrosis in BALB/c mice by inhibiting the NLRP3 inflammasome pathway ^[70]. Additionally, Zhang *et al.* (2022) observed that AS-IV (40 mg/kg/day) ameliorates myocardial fibrosis and hypertrophy in C57BL/6J mice with acute myocardial infarction, a mechanism attributed to the inhibition of the ROS/NLRP3/GSDMD signaling cascade, ultimately reducing apoptosis ^[71].

3.7. Anti-arrhythmic

Arrhythmia encompasses abnormalities in the origination of heart rhythm, the frequency and pattern of new beats, as well as impulse conduction, with a heightened prevalence observed in diverse organic cardiovascular disorders. Studies have demonstrated that HQ injection can postpone the impact of digitalis on arrhythmia by enhancing the functionality of Na⁺-K⁺-ATPase in myocardial tissue that is under inhibition ^[72]. Furthermore, AS-IV has been shown to markedly suppress the elongation of QRS duration and the augmentation of T wave amplitude, both of which are induced by toad venom in mice. This effect not only decreases the incidence of ventricular arrhythmias

but also significantly extends survival time, thereby exerting a protective role against toad venom-induced ventricular arrhythmias^[73].

4. The effects of Astragaloside IV on hemodynamics and toxicology

Research has conclusively established that AS-IV injection does not exert a noteworthy influence on partial thromboplastin time, blood enzyme time, or thrombin time in rabbits^[74]. Although AS-IV injection effectively diminishes whole blood viscosity in rabbits, its efficacious dosage range is comparatively constrained. Moreover, while AS-IV glycoside alters blood flow rheology in rabbits, this effect is moderately weak. Zhang *et al.* (2006) observed that over 83% of AS-IV binds to plasma proteins, showcasing a linear correlation within a concentration range of 250–1000 ng/mL^[75]. Notably, the elimination half-lives of AS-IV in male SD rats (administered at doses of 0.75, 1.5, and 3.0 mg/kg) were 98.1, 67.2, and 71.8 minutes, respectively, whereas, in female SD rats, they were 34.0, 66.9, and 131.6 minutes, respectively. Interestingly, there was no marked difference in the systemic clearance rate of AS-IV, indicating its potential for linear pharmacokinetic behavior within the experimental dosage range. Consistent with this, AS-IV exhibited linear pharmacokinetic characteristics in beagle dogs as well, with elimination half-lives of 51.9, 60.0, and 68.8 minutes in males and 62.9, 67.2, and 50.2 minutes in females at doses of 0.25, 0.5, and 1 mg/kg, respectively. The tissue distribution of AS-IV reveals a preferential accumulation in the lungs and liver, whereas its penetration into the brain is limited, possibly owing to the challenge of traversing the blood-brain barrier. Furthermore, 80% of AS-IV binds to serum proteins, and hepatic clearance is extremely slow, estimated at approximately 0.0041 kg/min. Zhang *et al.* (2006) delved into the excretion patterns of AS-IV following intravenous administration of 1.5 mg/kg in rats, uncovering that the total excretion through urine and feces in male rats amounted to 45.03% and 53.61%, respectively, indicating that approximately half of AS-IV undergoes *in vivo* metabolism^[75]. Additionally, in mice and dogs, AS-IV demonstrated a moderate to rapid clearance rate, maintaining linear kinetic properties within the dosage range of 0.75–3.0 mg/kg^[75].

Gu *et al.* (2004) conducted a comprehensive evaluation of the transport mechanisms and bioavailability of AS-IV^[76]. In mouse models, oral administration of AS-IV yielded suboptimal absorption, evidenced by absolute bioavailabilities of merely 3.66% and 2.2% across two distinct experimental settings^[76,77]. An *in vitro* study utilizing Caco-2 cells elucidated that the poor absorption of AS-IV primarily stems from its high molecular weight, low lipophilicity, and reliance on paracellular transport pathways^[78]. Zhang *et al.* (2007) similarly reported a modest absolute bioavailability of approximately 7.4% for AS-IV in beagle dogs^[79]. *In vivo* investigations further corroborated that AS-IV undergoes absorption primarily through passive diffusion mechanisms^[80]. Within a concentration range of 250 to 1000 ng/mL, the plasma protein binding rate of AS-IV approximates 90%. Nonetheless, the inherently low bioavailability of AS-IV poses significant limitations to its oral administration. To mitigate this challenge and enhance the oral bioavailability of AS-IV, the strategic design of its dosage forms is paramount. Several approaches have been proposed, including the utilization of chitosan, sodium deoxycholate, and AS-IV hydroxypropyl- β -cyclodextrin inclusion complexes, all of which have demonstrated potential to augment AS-IV absorption^[78,81].

Yu *et al.* (2007) conducted a subchronic toxicity study on *Astragalus membranaceus* extract (RAE) in SD rats and beagle dogs^[82]. Their findings indicate that RAE is deemed safe, without eliciting significant toxic side effects. Specifically, the safe dose range for SD rats was determined to be 5.7–39.9 g/kg, while for beagle dogs, it ranged from 2.85–19.95 g/kg, representing a 70- to 35-fold higher dose compared to the safe dose for humans. Additionally, the study explored the impact of AS-IV on embryonic development in rats and New Zealand white rabbits. In pregnant mice, a dose of 1.0 mg/kg AS-IV exhibited maternal toxicity, and doses exceeding 0.5 mg/kg

displayed embryotoxicity. However, no noteworthy visceral abnormalities or skeletal deformations were noted in either rats or New Zealand white rabbits ^[83].

Wan *et al.* (2010) conducted a comprehensive evaluation of the perinatal reproductive toxicity of AS-IV in SD rats, which did not uncover any clinical toxicity symptoms related to AS-IV in either male or female F0 rats throughout the pre-mating phase, the mating process, or during female pregnancy ^[84]. Furthermore, no notable differences were detected in the liver, kidneys, or reproductive organs of these rats. Following this, the study delved into the impact of AS-IV on the physiological and reflex development of F1 rats. Notably, a maternal dosage of 1.0 mg/kg/day of AS-IV significantly protracted the timelines for hair emergence, eye-opening, motor activity, and the cliff avoidance reflex. Conversely, memory and learning assessments failed to yield significant differences between the two groups.

In light of the anticipated human clinical dose of 10 mg/60 kg/day, it is paramount to gain a comprehensive understanding of the toxicity profile of AS-IV before its widespread clinical utilization. As a highly promising contender for novel drug development, further investigation is imperative to precisely delineate the effective and toxic dose ranges of AS-IV, taking into account its diverse therapeutic potential.

5. Conclusion and perspective

In summary, AS-IV demonstrates efficacy in ameliorating myocardial injury by mitigating oxidative stress, suppressing inflammatory responses and cell apoptosis, inhibiting myocardial cell hypertrophy, preventing myocardial fibrosis, and fostering angiogenesis. Furthermore, the multi-faceted and multi-target pharmacological effects of AS-IV glycoside align well with the intricate pathogenesis of various diseases, positioning it as a promising clinical candidate for the treatment of diseases and their associated complications. However, the development and clinical application of AS-IV as a novel drug face several challenges, primarily stemming from the complexity of its mechanism in treating cardiovascular diseases and the intricate network of its protective pathways. For instance, AS-IV (100 μ M) has been shown to hinder isoproterenol-induced myocardial fibrosis by inhibiting ROS-mediated MAPK activation, highlighting its ability to combat myocardial fibrosis through oxidative stress reduction ^[67]. Additionally, Liu *et al.* (2018) discovered that AS-IV (10 and 20mg/kg/day) mitigated myocardial hypertrophy, inflammatory responses, and cardiomyocyte apoptosis in C57BL6 mice by inhibiting the TBK1/PI3K/Akt pathway ^[85]. Meanwhile, AS-IV (40 and 80mg/kg/day) inhibited AAC-induced myocardial hypertrophy by upregulating the Nrf2/HO1 signaling pathway, indicating its antioxidant-mediated improvement of myocardial hypertrophy ^[86]. Zhang *et al.* (2021) further revealed that AS-IV (12.5 and 50 μ M) protects HL-1 mouse cardiomyocytes from ox-LDL-induced oxidative damage by inhibiting HDAC activity ^[87]. These findings underscore the potential of AS-IV as a therapeutic agent but also emphasize the need for further research to fully elucidate its mechanisms of action and optimize its clinical application.

Mechanistically, researchers have broadened their scope beyond the examination of traditional cellular signaling pathways to delve into the role of non-coding RNAs, particularly microRNAs (miRNAs) and circular RNAs, in the cardioprotective effects of AS-IV. miRNAs, which regulate gene expression post-transcriptionally, have garnered significant attention. Notably, miR-1 has emerged as an upregulated, muscle-specific miRNA in rats following myocardial infarction (MI) ^[88]. Wang *et al.* (2022) demonstrated that AS-IV (80 mg/kg) mitigated LPS (10 mg/kg)-induced cardiac dysfunction in SD rats by inhibiting miR-1-mediated inflammation and autophagy. This mechanism was recapitulated in vitro, where AS-IV (10 μ g/mL) alleviated LPS-induced damage in H9C2 cells through the same pathway ^[89].

As the field of non-coding RNA research continues to evolve, it becomes increasingly evident that

the cardioprotective effects of AS-IV may be partially mediated by miRNAs and circular RNAs. A more comprehensive and nuanced understanding of their diagnostic potential and regulatory functions within the cardiac system is gradually unfolding, offering fresh insights that could inform the expansion of AS-IV's clinical applications in cardiovascular diseases. This advancement holds promise for improving the prognosis of cardiovascular disease patients, thereby alleviating the financial and emotional burdens on society.

Hence, it is crucial to acknowledge that the multifaceted therapeutic effect of AS-IV, while promising, may also encompass potential side effects that could be inadvertently overlooked by researchers or remain undetected within the confines of shorter experimental timelines. Consequently, unraveling the direct targets of AS-IV's action is imperative. Presently, the precise direct target of AS-IV remains elusive. The exploration of direct targets for active components in traditional Chinese medicine (TCM) represents a pivotal research frontier that merits heightened attention in the future. To address this complexity, modern methodologies and technologies, including systems biology, network pharmacology, molecular docking, and drug target databases, can be harnessed to facilitate preliminary predictions of drug targets. Subsequently, these predictions can be rigorously validated through advanced techniques like surface plasmon resonance (SPR), isothermal titration calorimetry, and cellular thermal shift assay (CETSA), ensuring a robust understanding of AS-IV's mechanism of action. Moreover, it is paramount to recognize that the aforementioned research endeavors have yet to be substantiated in clinical settings. Therefore, future endeavors must persist in the pursuit of novel drug development and a deeper comprehension of AS-IV's mechanism of action, endeavors that have the potential to revolutionize therapeutic strategies for cardiovascular diseases, offering fresh perspectives and innovative solutions.

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Antiphospholipid Syndrome Misdiagnosed as Infective Endocarditis: A Case Report

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Abstract: This article presents a retrospective study of a case that was initially misdiagnosed as infective endocarditis but was later diagnosed as antiphospholipid syndrome (APS) upon further evaluation. The study aims to explore the clinical manifestations of APS and increase clinicians' awareness of its non-specific manifestations. The ultimate goal is to provide effective treatment as early as possible and prolong patients' survival.

Keywords: Antiphospholipid syndrome; Heart valves; Misdiagnosis

Online publication: January 13, 2025

1. Introduction

APS is a non-inflammatory autoimmune disease characterized by recurrent arterial and venous thrombosis, spontaneous abortions, and thrombocytopenia based on positive serum antiphospholipid antibodies. In recent years, the incidence and prevalence of APS have been overlooked, while its poor prognosis has always attracted much attention. Studies have shown that the 10-year mortality rate of APS patients is approximately 10%^[1-3]. Despite a relatively high survival rate, the 30% rate of permanent organ damage and disability cannot be ignored. Therefore, the diagnosis and treatment of APS have always been the focus of clinicians' work.

2. Medical records

A 42-year-old female patient presented to the emergency department of Yanbian University Hospital on October 17, 2023, with the chief complaint of "intermittent chest tightness and shortness of breath for 2 weeks, worsened by dyspnea for 2 days." The results of the cardiac color ultrasound indicate left heart enlargement, diffuse weakening of left ventricular (LV) systolic function, reduced LV diastolic function, severe aortic valve stenosis with insufficiency, and isoechoic area near the right coronary valve, possibly indicative of vegetation. The EF is 33%, the left atrial (LA) diameter is 43 mm, MPG is 77 mmHg, and the peak pressure gradient is 109 mmHg (**Figure 1**). Valvular heart disease with heart failure will cause the patient to experience occasional coughing and produce sputum. Additionally, the patient experienced a low-grade fever in the morning.

The patient has a history of hypertension and underwent two cesarean sections in 2018 and June 2023. On admission, physical examination revealed: temperature: 37.5°C; heart rate: 100 beats/min; respiratory rate: 15 breaths/min; blood pressure: 107/76 mmHg; no precordial bulge, apex beat located at 0.5cm to the left of the midclavicular line in the fifth intercostal space, no palpable thrills over the valve areas, regular rhythm, normal heart sounds, A2 > P2, systolic ejection murmur heard in the aortic valve area. Laboratory tests conducted after admission showed: cardiac markers: CK-MB 4.58 ng/mL, cTNI 0.62 ng/mL, MYO 35.62 ng/mL, NT-proBNP 14626.05 pg/mL, D-dimer 0.78 ug/mL, PCT 0.15 ng/mL. Coagulation time, blood routine, liver and kidney function, thyroid hormones, and tumor markers were all within normal ranges. The patient received treatment including nutritional support, vasodilators, and diuretics after admission. On October 20, 2023, a cardiovascular surgery consultation was requested to ascertain the cause. Considering the patient's recent cesarean section and occasional fever during illness, the possibility of "infective endocarditis" could not be ruled out. Blood cultures were negative. After improvement in the patient's condition, she was transferred to a higher-level hospital.

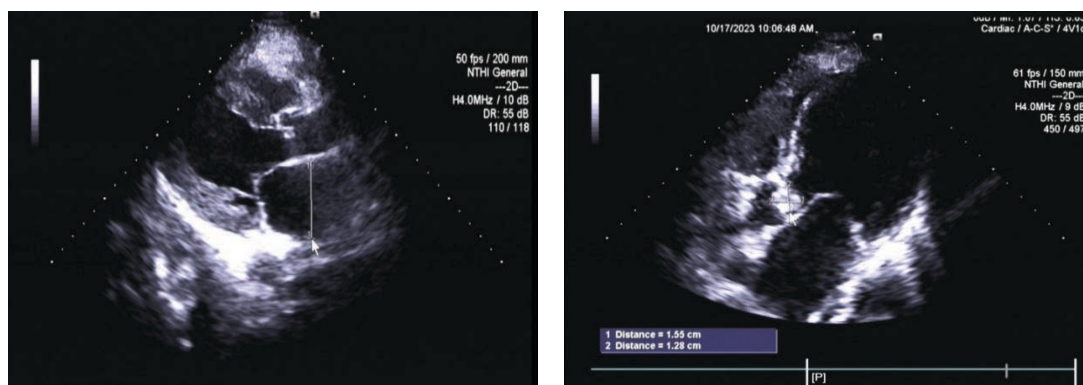


Figure 1. Cardiac color ultrasound.

On October 25, 2023, the patient underwent a cardiac color ultrasound at the Sixth Medical Center of the People's Liberation Army General Hospital. The results of the ultrasound showed that abnormal aortic valve function and elastic fibroma were considered, with possible vegetations not ruled out, severe aortic valve stenosis with moderate regurgitation was also observed, along with left heart enlargement and LV myocardial hypertrophy. Mildly reduced LV systolic function was noted, as well as moderate mitral valve regurgitation and mild tricuspid valve regurgitation. The LA measurement was 46 mm, the LV measurement was 54 mm, the interventricular septum was 14 mm, and the LV posterior wall was 14 mm. The patient sought treatment at Beijing Fuwai Hospital on October 26, 2023. Following admission, the medical team considered the possibility of infectious endocarditis based on the patient's symptoms and medical history. The Coronary CTA did not reveal any abnormalities. The transesophageal three-dimensional color ultrasound showed space-occupying lesions in the aortic valve, the nature of which is yet to be determined. The mitral valve showed small to moderate regurgitation, and there was left heart enlargement. Severe aortic valve stenosis and moderate regurgitation were also observed. The cardiac MRI scan revealed aortic valve nodules, which are more likely to be vegetations or thrombus. Additionally, severe aortic valve stenosis and mild to moderate regurgitation were observed. The cardiac MRI enhanced scan revealed the following:

- (1) High possibility of vegetations and thrombus due to aortic valve nodules, severe aortic valve stenosis, and mild to moderate regurgitation.
- (2) LV enlargement, left ventricular wall thickening, and decreased systolic function, which may indicate secondary changes.
- (3) Small focal fibrosis was found scattered in the LV endocardium.

The results of the three-day blood culture were negative, indicating that infective endocarditis is not supported by current evidence. To further identify the underlying cause, comprehensive blood tests (**Table 1**) showed no abnormalities in blood routine, biochemistry, vasculitis markers, or antinuclear antibody spectrum. On November 9, 2023, consultation was sought from the Rheumatology and Immunology Department at Peking University People's Hospital due to abnormal indicators in the patient's medical history of rheumatic conditions and immune-related issues. Based on the patient's severe aortic valve stenosis, positive results for anticardiolipin antibodies, anti- β 2 glycoprotein, and lupus anticoagulant, as well as a history of early pregnancy miscarriage and the presence of livedo reticularis on physical examination, combined with endocardial biopsy findings (**Figure 2**), the diagnosis of "antiphospholipid syndrome" was confirmed. The patient presented with fever and cough with sputum production, suggesting pulmonary inflammation secondary to antiphospholipid syndrome. Warfarin, heparin, and other anticoagulants are administered to prevent thrombosis, while prednisone is used to reduce inflammation. The blood tests were reviewed, and the lupus anticoagulant SCT standardized ratio (SCT-R) was found to be 1.82, anti- β 2 glycoprotein 1IgG (β 2GP1 IgG) was 101.00 AU/mL, and anti- β 2glycoprotein 1IgM (β 2GP1 IgM) was 28.70 AU/mL. The abnormal indicators were higher than before, but the recovery was effective.

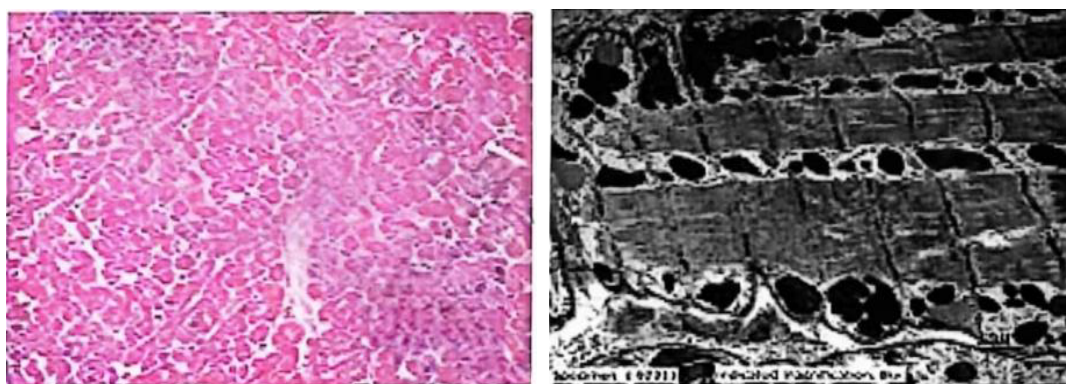
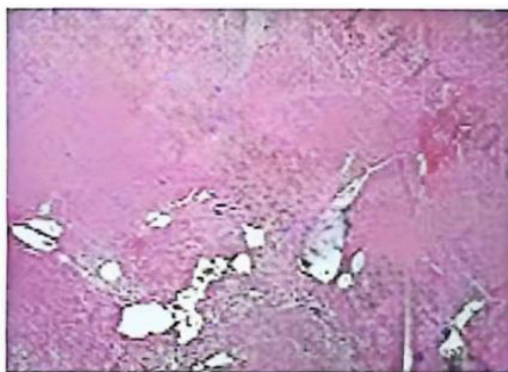
To improve the patient's symptoms, cardiac surgery was performed on December 7, 2023. The procedure involved general anesthesia, hypothermia, and extracorporeal circulation to replace the aortic valve. The diseased valve was replaced with a Regent 19# aortic valve mechanical valve using interrupted sutures. The procedure was successful. Follow-up echocardiography showed an ejection fraction of 53%, an LV measurement of 50 mm, and an LA measurement of 34mm. The mechanical valve functioned normally after the aortic valve replacement. The postoperative pathology report (**Figure 3**) revealed chronic valvulitis (aortic valve) with non-infectious thrombotic vegetation formation. The patient was diagnosed with: (1) valvular disease, atypical verrucous endocarditis (Libman-Sacks), severe aortic valve stenosis, aortic valve vegetations; (2) heart failure; (3) APD. Treatment included oral prednisone 50 mg/d, low-molecular-weight heparin (warfarin added later, initial dose 3 mg/d), atenolol, torasemide, and irbesartan to improve cardiac remodeling and control blood pressure. The general condition of the patient improved and stabilized after the procedure. After discharge, the patient's condition remained stable and prednisone acetate dosage was reduced to 30 mg/d. The patient continued to take warfarin tablets 3 mg/d, atenolol 12.5 mg/d, torsemide 20 mg/d, and irbesartan 37.5 mg/d orally.

Table 1. Comprehensive blood tests

Subject	Result	Unit	Range
ASO	63.5	IU/mL	0–200
CRP	12.3	mg/L	0–8
RF	< 20.00	IU/mL	0–20
IgG	13.4	g/L	7.23–16.85
IgA	2.34	g/L	0.69–3.82
IgM	1.09	g/L	0.63–2.77
IgE	10.3	IU/mL	0–165
C3	0.95	g/L	0.85–1.93
C4	0.208	g/L	0.12–0.36
ACL IgG	> 120.00	GPLU/mL	negative: < 8; positive: \geq 12

Table 1 (Continued)

Subject	Result	Unit	Range
ACL IgM	10.30	MPLU/mL	negative: < 8; positive: ≥ 12
β2GP1 IgG	162.00	AU/mL	negative: < 16; positive: ≥ 24
β2GP1 IgM	46.30	AU/mL	negative: < 16; positive: ≥ 24
SCT-S	3.99		
SCT-C	1.13		
SCT-R	3.54		0–1.16
DRVVT-S	2.03		
DRVVT-C	1.10		
DRVVT-R	1.85		0–1.2

**Figure 2.** Endocardial biopsy.**Figure 3.** Postoperative pathology report.

3. Follow-up

The patient's six-month follow-up data after discharge showed no occurrence of thrombosis or thrombocytopenia.

4. Discussion

Studies have shown that patients with elevated antiphospholipid antibodies have an increased risk of developing

Libman-Sacks endocarditis ^[4]. As a result, when APS affects the heart, it is more likely to cause valvular disease, particularly on the left side of the heart, such as the mitral valve, while right coronary valve disease is less common ^[5-7]. The patient experienced a sudden onset of symptoms, including heart failure, vegetations on the right coronary valve, and Libman-Sacks endocarditis. The admission auxiliary examinations yielded positive results for anticardiolipin antibodies, anti- β_2 glycoprotein, and lupus anticoagulant. The heart color prompts the formation of heart valve vegetation. The electrocardiogram and cardiac MRI did not show any obvious signs of myocardial ischemia. The coronary CTA showed no coronary vascular stenosis. The heart valve biopsy and postoperative pathology revealed the formation of chronic valvulitis and non-inflammatory thrombotic vegetations. The pathogenesis of this disease involves the linear deposition of low IgG anticardiolipin antibodies in cardiac valve endothelial cells. APS presents with an acute onset of cardiac involvement and severe symptoms. If examinations reveal unexplained intracardiac thrombus, valve involvement, myocardial ischemia, or other changes, APS should be considered, and further examinations should be performed to ensure timely diagnosis and treatment ^[8].

Female APS patients commonly experience morbid pregnancy symptoms such as recurrent miscarriage, eclampsia, preeclampsia, intrauterine distress, intrauterine growth retardation, stillbirth, or premature birth. Placental thrombosis is considered the main cause of APS in most cases, and its pathogenesis involves various cells and factors. Research indicates that APS has an incidence rate of 0.75/100,000 to 2.1/100,000 and a prevalence rate of 6.19/100,000 to 50/100,000. The highest incidence rate in women occurs between the ages of 30–39 and 70–79. APS is considered to be the cause of recurrent early miscarriage in 15% of patients ^[5]. In this case, the cause of the multiple failed pregnancies remains to be verified, and it is unclear whether APS is related. Therefore, patients who experience unexplained pregnancy loss should be tested for various autoantibodies, particularly antiphospholipid antibodies, before attempting another pregnancy. This will help determine if medication is necessary to improve their immune system and protect the health and well-being of both the mother and fetus.

Additionally, there are atypical manifestations that may be overlooked, such as skin rashes, redness, and reticular erythema. Damage to the lungs commonly includes pulmonary embolism and pulmonary infarction. Repeated pulmonary vascular thrombosis can lead to pulmonary hypertension, as well as rare conditions such as acute respiratory distress syndrome, intra-alveolar hemorrhage, pulmonary capillaritis, and alveolar fibrosis ^[6]. The patient exhibited reticular erythema and pneumonia during the disease. Several sputum tests revealed a small number of Gram-positive cocci. Although pulmonary inflammation is considered a likely factor, there is no direct evidence linking APS to pulmonary inflammation.

5. Conclusion

In summary, due to the ongoing advancements in medical technology, clinical subfields are becoming increasingly specialized. As a result, specialist doctors may lack knowledge of rare diseases in other disciplines, making it challenging to provide comprehensive diagnosis and treatment for complex cases. Furthermore, APS patients can experience rapid progression and damage to multiple systems. In this particular case, the patient's primary symptoms were chest tightness and shortness of breath. Clinicians typically only consider common causes of circulatory and respiratory issues, which can lead to misleading early diagnoses. The development and promotion of medical imaging and testing technology have played a significant role in advancing diagnosis and treatment methods ^[9,10]. The diagnosis of the disease in this case was based on the professional judgment of clinicians and supported by detection methods such as endocardial pathology and anticardiolipin antibodies.

Clinicians need to consider the possibility of autoimmune diseases in young patients with multi-system damage in the future, perform necessary laboratory examinations and thorough analysis promptly to attain early diagnosis and treatment, thereby reducing the incidence of missed diagnosis and misdiagnosis.

Disclosure statement

The authors declare no conflict of interest.

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Clinical Effect of Buyang Huanwu Decoction Combined with Acupuncture in Treating Cerebral Infarction Sequelae

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Abstract: *Objective:* To explore the clinical effect of Buyang Huanwu Decoction combined with acupuncture in treating cerebral infarction sequelae. *Methods:* In this study, 80 patients with cerebral infarction sequelae admitted to the hospital from April 2022 to March 2024 were selected and divided into a control group ($n = 40$) and a combined group ($n = 40$) according to different treatment regimens. The control group received acupuncture treatment alone, while the combined group received Buyang Huanwu Decoction treatment based on the control group. The clinical effects, physical indicators, and adverse reactions of the two groups were compared and observed 3 months after treatment. *Results:* After treatment, the clinical efficacy of the combined group (92.50%) was significantly higher than that of the control group (72.50%) ($p < 0.05$). The physical indicators of the combined group were significantly better than those of the control group ($p < 0.05$). Additionally, the combined group had fewer adverse events than the control group ($p < 0.05$). *Conclusion:* The combination of Buyang Huanwu Decoction and acupuncture has significant efficacy in treating cerebral infarction sequelae. It can effectively contain disease progression, reduce adverse events, and significantly improve patients' physical indicators. This treatment approach has clinical promotional value.

Keywords: Buyang Huanwu Decoction; Acupuncture; Cerebral infarction sequelae; Clinical efficacy

Online publication: January 10, 2025

1. Introduction

Cerebral infarction is caused by insufficient blood supply to certain brain regions due to various reasons, leading to ischemia, hypoxia, and cell necrosis. Clinically, it manifests as varying degrees of neurological dysfunction. As the disease progresses, patients may develop sequelae such as limb movement difficulties, crossed paralysis, memory loss, visual field defects, and language difficulties^[1]. Traditional Chinese medicine has shown significant efficacy in treating cerebral infarction sequelae. The combined application of traditional Chinese medicine and various techniques of traditional Chinese medicine is helpful for patients' functional recovery, and its intervention value cannot be ignored^[2]. In the clinical practice of traditional Chinese medicine, acupuncture is a commonly used treatment for such sequelae. It has a long history in China. Buyang Huanwu

Decoction has the effect of promoting blood circulation and nourishing blood, removing blood stasis without damaging the blood condition, and dredging meridians^[3]. Therefore, this study explores the clinical effect of Buyang Huanwu Decoction combined with acupuncture in treating cerebral infarction sequelae. The report is as follows.

2. Materials and methods

2.1. General information

In this study, 80 patients with cerebral infarction sequelae admitted to the hospital were selected as the research subjects. They were divided into a control group and a combined group based on the differences in treatment methods, with 40 patients in each group. The combined group consisted of 22 males and 18 females, aged between 52 and 83 years old, with an average age of (72.19 ± 8.55) years old and a disease duration of (2.11 ± 0.38) months. The control group consisted of 21 males and 19 females, aged between 54 and 81 years old, with an average age of (72.74 ± 8.32) years old and a disease duration of (2.18 ± 0.37) months. All patients (or/and) their families were fully informed and voluntarily chose to participate in this research activity. There was no significant difference between the two groups ($P > 0.05$). This study was approved by the ethics committee of the hospital.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Meet the diagnostic criteria of traditional Chinese medicine^[4], mainly manifesting as symptoms such as unclear speech, facial distortion, and hemiplegia, followed by dizziness, persistent coughing, severe headache, and imbalance of body; (2) Meet the diagnostic criteria of western medicine confirmed by MRI or CT; (3) Age over 40 years.

Exclusion criteria: (1) Presence of contraindications to medication; (2) Clear organic damage to major internal organs such as the heart, liver, and kidneys; (3) Presence of brainstem infarction or hemorrhage; (4) Complete loss of consciousness; (5) Presence of malignant tumors.

2.3. Methods

The control group received a single acupuncture treatment: 0.25 mm Hua Tuo brand acupuncture needles (National Medical Device Registration Number: 201662270970) were used. The primary acupoints included Juegu (GB39), Sishencong (EX-HN1), and Baihui (GV20). The acupoints were selected based on the symptoms: for phlegm and blood stasis obstructing collaterals, Zhongwan (CV12), Hegu (LI4), Fenglong (ST40), Danzhong (CV17), Taichong (LR3), and Yanglingquan (GB34) were added; for Qi deficiency and blood stasis, Zusanli (ST36), Taichong (LR3), Qimen (LR14), Hegu (LI4), and Yanglingquan (GB34) were selected; for oral and ocular distortion, Jiache (ST6), Yingxiang (LI20), Taichong (LR3), Dicang (ST4), Hegu (LI4), and Xiaguan (ST7) were chosen; for flaccid paralysis of lower limbs, Fengshi (GB31), Yanglingquan (GB34), Zusanli (ST36), and Huantiao (GB30) were the acupoints. Acupuncture was performed on bilateral main acupoints and corresponding syndrome-specific acupoints daily, focusing on the affected side. The needles were retained for 30 minutes. The treatment was continuous for 30 days.

The combined group received “Buyang Huanwu Decoction” based on the control group’s treatment. The medicinal herbs included 30 g of Huangqi (Astragalus), 15 g each of Honghua (Safflower), Taoren (Peach Kernel), Chuanxiong (Szechuan Lovage Rhizome), Danggui (Chinese Angelica), and Dilong (Earthworm), and 10 g of Chishao (Red Peony Root). The dosage was adjusted according to the severity of the symptoms. For patients with Qi and blood deficiency, Dangshen (Pilose Asiabell Root) was added appropriately; for patients

with constipation, Xingren (Almond) was used in combination, but excessive amounts should be avoided to prevent uncontrolled bowel movements; for patients with incontinence, Jinyingzi (Cherokee Rose Fruit) was added; for patients with edema of the limbs, the dosage of Fuling (Poria) was increased to promote urination and reduce swelling. The above medicinal herbs were mixed and decocted with cold water to 300 mL. 100 mL was taken each time, three times a day. Nine days constituted one course of treatment, and three consecutive courses were administered.

2.4. Observation indicators

Observation and analysis of the efficacy, physical data, and adverse reactions of the two groups were conducted before and 3 months after treatment.

- (1) Clinical effect: The resolution of symptoms, clinical signs, and functional improvement in each group were observed. A significant effect was defined as the disappearance or significant reduction (greater than or equal to 30%) of the lesion, accompanied by a notable improvement in patient function. Effective was defined as a moderate reduction in lesion size between 30–60%, with slight improvement in clinical symptoms and signs but not complete resolution. Ineffective was defined as no significant reduction in the lesion and inability to perform daily activities independently. The overall clinical effect was calculated as [(significant effect + effective) / total number of cases] × 100%.
- (2) Physical indicators: Physical indicators of the two groups were compared and observed before and 3 months after treatment using the Activity of Daily Living Scale (ADL), with scores positively correlated to daily living abilities (maximum score of 50); the Barthel Index (BI), with scores positively correlated to activity abilities (maximum score of 100); and the National Institute of Health Stroke Scale (NIHSS), with scores negatively correlated to indicators (maximum score of 10).
- (3) Adverse reactions: Adverse reactions during treatment, including fatigue, nausea, and dizziness, were observed and compared between the two groups. The total incidence of adverse reactions was calculated as [(fatigue + nausea + dizziness) / total number of cases] × 100%.

2.5. Statistical methods

The data obtained in this study, including normally distributed measurement data (t) and count data (χ^2), were analyzed using SPSS 24.0 statistical software. Measurement data were expressed as mean ± standard deviation (SD) and count data were expressed as (n, %). If $p < 0.05$, the results were considered statistically significant.

3. Results

3.1. Comparison of clinical effects between the two groups

After treatment, the significant effectiveness rate of the combined therapy intervention was 92.50%, which was significantly better than the 72.50% in the control group ($p < 0.05$). See **Table 1** for details.

Table 1. Comparison of clinical effects between the two groups [n(%)]

Groups	n	Efficient	Effective	Ineffective	Total clinical outcome
Control group	40	21	11	11	72.50
Combined GROUP	40	28	9	3	92.50
χ^2					5.541
p					0.018

3.2. Comparison of physical indicators between the two groups of patients

Before treatment, there is no more significant difference between the physical indicators of the two groups of patients ($p > 0.05$); after the end of treatment, the combined therapy is significantly better than monotherapy ($p < 0.05$). See **Table 2**.

Table 2. Comparison of physical indicators before and after treatment of the two groups of patients (mean \pm SD)

Groups	<i>n</i>	ADL		BI index		NIHSS	
Control group	40	58.29 \pm 1.21	65.38 \pm 1.78*	21.52 \pm 6.43	45.12 \pm 9.21*	6.21 \pm 1.78	4.78 \pm 1.42*
Combined group	40	58.22 \pm 1.18	74.14 \pm 1.98*	21.51 \pm 5.78	55.78 \pm 10.78*	6.19 \pm 1.56	3.12 \pm 1.98*
χ^2		0.262	20.808	0.007	4.755	0.053	4.308
<i>p</i>		0.794	< 0.001	0.994	< 0.001	0.957	< 0.001

Note: Compared with the same group before treatment, * $p < 0.05$.

3.3. Comparison of the occurrence of adverse reactions between the two groups of patients

The combined group had a significant reduction in their adverse events after treatment ($p < 0.05$). See **Table 3**.

Table 3. Comparison of the occurrence of adverse reaction events between the two groups of patients [$n(\%)$]

Groups	<i>n</i>	Fatigue	Regurgitation	Dizziness	Total adverse event occurrence
Control group	40	2	2	3	17.50
Combined group	40	1	0	0	2.50
χ^2					5.000
<i>p</i>					0.025

4. Discussion

Cerebral infarction originates from the obstruction of blood supply to the brain, leading to neuron damage due to hypoxia. After the onset of the disease, patients' physical activities and central nervous system will be severely affected, leaving many sequelae and significantly reducing their quality of life [8]. Common sequelae of cerebral infarction include language communication disorders, accompanied by limb movement disorders, nervous system dysfunction, including dysphagia, bowel and bladder control disorders, and visual impairment [9]. At this stage, modern medicine has not determined an effective method to cure the sequelae of cerebral infarction and can only control symptoms through medication, with poor efficacy. Therefore, in recent years, the treatment direction for the sequelae of cerebral infarction has shifted to traditional Chinese medicine therapies. In traditional Chinese medicine, cerebral infarction is explained as caused by imbalances of Yin and Yang, weakness of healthy Qi, and disorders of Qi and blood, leading to damage of brain collaterals and obstruction of brain vessels. Although symptoms can be alleviated with appropriate treatment, the loss of Qi remains significant, and there is still residual blood stasis in the brain, which further damages brain collaterals and complicates the condition. Therefore, traditional Chinese medicine advocates that the treatment of sequelae of cerebral infarction should follow the principles of promoting blood circulation to remove blood stasis and nourish Qi and blood [10].

Buyang Huanwu Decoction, created by famous Qing Dynasty physician Wang Qingren, combines the treatment methods of removing blood stasis and nourishing Qi and blood. It has demonstrated significant

efficacy in the treatment of cerebral infarction and has been affirmed by modern medicine. The main ingredient of this formula is *Astragalus membranaceus*, which has the effect of nourishing Qi. It also contains earthworm, peach kernel, Chuanxiong rhizome, safflower, and red peony root, which have the functions of promoting blood circulation to remove blood stasis, relieving pain and anti-inflammatory effects, relaxing muscles and activating collaterals, as well as *Polygala tenuifolia* and *Acorus tatarinowii*, which can promote blood circulation and Qi flow. The entire formula is designed to nourish Qi and promote blood circulation, dredge meridians and activate collaterals. Modern medical research has further confirmed that this formula has significant effects on vasodilation, thrombolysis, and anticoagulation, and can effectively reduce blood viscosity. Acupuncture, as a unique diagnostic and treatment method of traditional Chinese medicine, not only helps to dredge the brain's meridians and collaterals by stimulating acupoints but also significantly adjusts cerebral blood flow. It can further improve neurotransmitter transmission function, promote the repair and regeneration of damaged neurons, and thus enhance neurological activity ^[11]. Furthermore, studies have found that Buyang Huanwu Decoction has the effects of nourishing the liver and kidney, promoting blood circulation and dredging veins, and maintaining homeostasis. Combining Buyang Huanwu Decoction with acupuncture can not only soothe the patient's brain, reduce intracranial pressure, and improve organ function deficiency, but also enhance the patient's immune metabolism, significantly slow down neuronal apoptosis, achieve treatment effects and obtain good results ^[12,13].

Before treatment, there were no significant differences in various physical indicators between the two groups of patients ($p > 0.05$). In this study, the clinical efficacy of 92.50% is similar to the research results of Wu *et al.* (2022) ^[14], which is 89.19%. After treatment, the combined group of patients showed significant improvement compared to the control group ($p < 0.05$). The reason for this is that acupuncture, as one of the traditional Chinese medicine rehabilitation therapies, has significant efficacy in the treatment of cerebral infarction sequelae. Combined with Buyang Huanwu Decoction, it has the effects of promoting blood circulation to remove blood stasis, benefiting the liver and strengthening the kidneys, which helps to improve the body's immune system and blood circulation efficiency, thereby achieving the goal of improving various physical indicators of patients. After treatment, the incidence of adverse events in the combined group was lower than that in the control group ($p < 0.05$). The reason is that the main acupuncture points selected in this study include Juegu, Sishencong, and Baihui, which help to regulate Qi and blood and relax the meridians and tendons. Appropriate adjustments and combinations are made based on the symptoms, and individualized acupuncture treatment plans are implemented. Through the combination of oral Chinese medicine and acupuncture therapy, it can improve the efficiency of blood flow in the body, gradually improve the microcirculation of the brain, ensure the supply of neuronutrition, and have a good effect on sequelae, improving patients' physical indicators while reducing the occurrence of adverse events ^[15].

5. Conclusion

In summary, the combination of Buyang Huanwu Decoction and acupuncture has significant effects on cerebral infarction sequelae, which can control the progression of the disease, delay deterioration, reduce complications, and improve patients' physiological parameters. It has the potential for clinical application and promotion.

Disclosure statement

The authors declare no conflict of interest.

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Analysis of the Adjuvant Therapeutic Effect of Epalrestat Tablets in Enhancing the Treatment of Diabetic Complications

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Abstract: *Objective:* To evaluate the adjuvant therapeutic effect of Epalrestat tablets on diabetic complications. *Methods:* 96 patients with diabetic complications who were admitted to the hospital from September 2021 to September 2023 were selected and randomly divided into two groups using a random number table. The observation group was treated with Epalrestat tablets combined with Ginkgo Dipyrindolum Injection, while the control group was treated with Ginkgo Dipyrindolum Injection only. The total effective rate, blood glucose indicators, oxidative stress indicators, and adverse reaction rates were compared between the two groups. *Results:* The total effective rates of diabetic nephropathy (DN), diabetic foot (DF), and diabetic peripheral neuropathy (DPN) in the observation group were higher than those in the control group ($P < 0.05$). After 12 weeks of treatment, the blood glucose indicators in the observation group were lower than those in the control group, and the oxidative stress indicators were better than those in the control group ($P < 0.05$). The adverse reaction rate in the observation group was lower than that in the control group ($P < 0.05$). *Conclusion:* Epalrestat tablets can assist in improving the clinical efficacy of patients with diabetic complications, lowering their blood glucose levels, reducing oxidative stress damage, and decreasing adverse reactions after medication.

Keywords: Epalrestat tablets; Diabetic complications; Adjuvant therapy

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1. Introduction

The high incidence of diabetes is related to factors such as changes in dietary structure, changes in the living environment, and increased work pressure. It is a metabolic chronic disease characterized by continuous elevation of blood glucose, and its progression can affect renal function, foot function, and peripheral nerves, leading to various complications. At this stage, the main treatment for diabetic complications is symptomatic drug therapy, to improve complication symptoms and reduce their long-term harm. Among them, Ginkgo Dipyrindolum Injection is a commonly used therapeutic drug for this disease, which can expand coronary and cerebral blood vessels, and improve vascular wall tension, thereby reducing vascular permeability and correcting ischemia and other manifestations ^[1]. However, the effectiveness of single-drug treatment with this medication is

not satisfactory, and it needs to be combined with other drugs. Epalrestat tablets are commonly used aldose reductase inhibitors that can inhibit multiple pathways of protein kinase C signaling, increase carbon monoxide production, and thus protect neurovascular function and improve overall efficacy ^[2]. Based on this, this study selected 96 patients with diabetic complications to evaluate the therapeutic effect of Epalrestat tablets.

2. Materials and methods

2.1. General information

96 patients with diabetic complications admitted to the hospital between September 2021 and September 2023 were selected and randomly divided into two groups using a random number table. The observation group consisted of 48 patients, including 27 males and 21 females, aged between 40 and 78 years old with a mean age of (52.65 ± 4.19) years old. The duration of diabetes ranged from 1 to 10 years with a mean of (5.84 ± 0.97) years. The types of complications included 19 cases of DN, 16 cases of DF, and 13 cases of DPN.

The control group also consisted of 48 patients, including 28 males and 20 females, aged between 41 and 79 years old with a mean age of (52.91 ± 4.32) years old. The duration of diabetes ranged from 2 to 10 years with a mean of (5.91 ± 0.90) years. The types of complications included 18 cases of DN, 16 cases of DF, and 14 cases of DPN. There was no statistically significant difference in basic information between the two groups ($P > 0.05$).

Inclusion criteria: age < 80 years old; normal cardiac, liver, and kidney function; normal mental state; meeting medication indications; informed consent for the study.

Exclusion criteria: patients with malignant tumors or infectious diseases; patients with major organ parenchymal diseases; incomplete clinical data; allergy to study drugs; withdrawal from the study.

2.2. Methods

Both groups of patients followed a low-sugar, low-salt, and low-fat diet, with moderate daily exercise to control blood glucose levels. If the patient's HbA1c level was less than 7%, they were administered vitamin B1 orally at a dose of 20 mg three times a day, combined with adenosine cobalamin at a dose of 0.5 mg three times a day for 12 weeks.

The control group was treated with Ginkgo Dipyrindolum Injection at a dose of 20 mL mixed with 250 mL of 0.9% sodium chloride solution, administered via intravenous infusion once daily for 12 weeks.

The observation group was treated with Epalrestat tablets combined with Ginkgo Dipyrindolum Injection. The usage and dosage of Ginkgo Dipyrindolum Injection were the same as above. Epalrestat tablets were administered orally at a dose of 50 mg three times a day for 12 weeks.

2.3. Observation indicators

- (1) Blood glucose indicators: Fasting blood glucose (FBG), HbA1c, and 2-hour postprandial blood glucose (2hPG) were measured before and after treatment.
- (2) Oxidative stress indicators: Venous blood was drawn before and after treatment, and superoxide dismutase (SOD), malondialdehyde (MDA), and reactive oxygen species (ROS) were measured using enzyme-linked immunosorbent assay.
- (3) Adverse reactions: Adverse reactions such as nausea and vomiting, diarrhea and abdominal pain, dizziness, loss of appetite, and skin irritation were observed.

2.4. Evaluation criteria for therapeutic effect

- (1) DN: Significant effect: asymptomatic or mild symptoms, no abnormality in Cr-C, and a decrease in

UAE of more than 30%; Initial effect: moderate symptoms, mild abnormality in Cr-C, and a decrease in UAE of 10% to 30%; No effect: severe symptoms, severe abnormality in Cr-C, and a decrease in UAE of less than 10%.

- (2) DF: Significant effect: healing of ulcer surface or healing degree > 80%, specific decrease in Wagner grade ≥ 2 ; Initial effect: healing degree of ulcer surface between 50% and 80%, specific decrease in Wagner grade by 1; No effect: healing degree of ulcer surface < 50%, no change in Wagner grade.
- (3) DPN: Significant effect: no pain in limbs, normal motor and sensory functions; Initial effect: mild pain in limbs, improvement in motor and sensory functions; No effect: no change in limb pain, motor and sensory functions.

2.5. Statistical analysis

Data processing was performed using SPSS 28.0 software. Measurement data were expressed as mean \pm standard deviation (SD) and compared and tested using *t*-values. Count data were expressed as (n/%) and compared and tested using chi-square (χ^2) values. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Comparison of total effective rates between the two groups

The total effective rates of DN, DF, and DPN in the observation group were higher than those in the control group ($P < 0.05$). See **Table 1–3** for details.

Table 1. Comparison of total effective rates of DN between the two groups (n/%)

Subgroups	<i>n</i>	Remarkable results	Initial effect	No effect	Overall effective
Observation group	19	10	8	1	94.74 (18/19)
Control group	18	7	5	6	66.67 (12/18)
χ^2					4.748
<i>P</i>					0.029

Table 2. Comparison of the overall DF effectiveness rate between the two groups of patients (n/%)

Subgroups	<i>n</i>	Remarkable results	Initial effect	No effect	Overall effective
Observation group	16	8	6	2	87.50 (14/16)
Control group	16	5	3	8	50.00 (8/16)
χ^2					5.236
<i>P</i>					0.022

Table 3. Comparison of the overall DPN efficiency of the two groups of patients (n/%)

Subgroups	<i>n</i>	Remarkable results	Initial effect	No effect	Overall effective
Observation group	13	7	5	1	92.31 (12/13)
Control group	14	4	4	6	57.14 (8/14)
χ^2					4.340
<i>P</i>					0.037

3.2. Comparison of blood glucose indexes between the two groups of patients

Before treatment, there is no difference in the comparison of blood glucose indicators between the two groups ($P > 0.05$). After 12 weeks of treatment, the blood glucose index of the observation group was lower than that of the control group ($P < 0.05$) (Table 4).

Table 4. Comparison of blood glucose indexes between the two groups of patients (mean \pm SD)

Subgroups	<i>n</i>	FBG (mmol/L)		HbA1c (%)		2hPG (mmol/L)	
		Before treatment	After treatment	b	After treatment	Before treatment	After treatment
Observation group	48	6.35 \pm 1.91	4.31 \pm 0.58	11.48 \pm 2.03	7.10 \pm 1.27	12.37 \pm 2.07	7.30 \pm 1.25
Control group	48	6.38 \pm 1.99	5.24 \pm 0.67	11.41 \pm 2.09	8.49 \pm 1.34	12.31 \pm 2.04	9.31 \pm 1.29
<i>t</i>		0.075	7.271	0.166	5.216	0.143	7.753
<i>P</i>		0.940	0.000	0.868	0.000	0.887	0.000

3.3. Comparison of oxidative stress indicators between the two groups of patients

Before treatment, there was no difference in the comparison of oxidative stress indicators between the two groups ($P > 0.05$). After 12 weeks of treatment, the oxidative stress indicators of the observation group were better than those of the control group ($P < 0.05$) (Table 5).

Table 5. Comparison of oxidative stress indicators between the two groups of patients (mean \pm SD)

Subgroups	<i>n</i>	SOD (μ g/mL)		MDA (mmol/mL)		ROS (μ mol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	48	53.69 \pm 4.61	86.95 \pm 6.19	15.67 \pm 2.06	33.18 \pm 2.41	822.16 \pm 19.75	315.93 \pm 22.07
Control group	48	53.54 \pm 4.68	70.18 \pm 6.10	15.60 \pm 2.04	24.86 \pm 2.13	820.53 \pm 19.79	257.61 \pm 21.19
<i>t</i>		0.158	13.369	0.167	17.922	0.404	13.206
<i>P</i>		0.875	0.000	0.868	0.000	0.687	0.000

3.4. Comparison of the adverse reaction rate of patients in the two groups

The adverse reaction rate of patients in the observation group was lower than that of the control group ($P < 0.05$) (Table 6).

Table 6. Comparison of the adverse reaction rate of patients in the two groups (*n*/%)

Subgroups	<i>n</i>	Nausea and vomiting	Diarrhea and abdominal pain	Dizziness	loss of appetite	Skin allergy	Incidence
Observation group	48	1	0	0	1	0	4.17 (2/48)
Control group	48	2	2	1	2	1	16.67 (8/48)
χ^2							4.019
<i>P</i>							0.045

4. Discussion

There are various types of diabetic complications, such as diabetic nephropathy (DN) and diabetic foot (DF), which increase the difficulty of diabetes treatment, exacerbate disease-related pain, elevate the disability rate, and affect patients' treatment prognosis. Currently, Ginkgo Dipyridolum Injection is a fundamental medication for diabetic complications, capable of stabilizing blood glucose levels and inhibiting the progression of complications^[3,4]. Ginkgo Dipyridolum, a compound preparation containing drug components like ginkgo and dipyridolum, can dilate blood vessels, block the reuptake process of adenosine by epithelial cells or platelets, reduce phosphodiesterase content, and prevent the massive generation of Thromboxane A2. Therefore, it has fewer side effects and can prevent diabetic cardiovascular and cerebrovascular complications. However, long-term and high-dose administration of Ginkgo Dipyridolum can lead to adverse reactions, necessitating the combination of auxiliary drugs that are both effective and safe^[5].

Epalrestat serves as an adjuvant therapeutic drug for diabetic complications. Its mechanism for the prevention and treatment of this disease involves reducing the efficiency of rapid conversion of glucose into aldose reductase during the polyol metabolism process, enabling sorbitol to fully exert its protective effect on neuronal function, preventing the accumulation of neurons, and thereby improving diabetic peripheral neuropathy symptoms and preventing peripheral nerve disorders^[6]. This drug inhibits the pathogenesis of multiple diabetic complications and can act on various substance generation processes such as protein kinase C, polyol pathway, and advanced glycation end products, thus delaying the onset of diabetic complications and achieving better therapeutic effects^[7].

The results showed that the total effective rates of DN, DF, and diabetic peripheral neuropathy (DPN) in the observation group were higher than those in the control group ($P < 0.05$). The reason is that Epalrestat can alleviate symptoms such as paresthesia and limb numbness, effectively stabilize blood glucose levels, prolong the half-life of Ginkgo Dipyridolum Injection, increase its plasma concentration, and thereby fully exert the drug's efficacy and enhance the effectiveness of treatment^[8]. The blood glucose level in the observation group after treatment was lower than that in the control group ($P < 0.05$). This is because Epalrestat can indirectly inhibit insulin resistance and reduce the degree of neuropathy, assisting patients in effectively lowering blood glucose. Additionally, this drug can reduce the absorption efficiency of carbohydrates by small intestinal tissue, thus lowering postprandial blood glucose levels^[9]. The oxidative stress indicators in the observation group after treatment were better than those in the control group ($P < 0.05$). The reason is that Epalrestat selectively inhibits aldose reductase, reaches peak plasma concentration within 1 hour of administration, and can reduce the intracellular sorbitol accumulation rate in neurons through the polyol pathway. This prevents inflammatory factors from continuously damaging renal tissue or nerve blood vessels, thereby reducing oxidative stress reactions^[10]. The adverse reaction rate in the observation group was lower than that in the control group ($P < 0.05$). This is because Epalrestat can enhance the utilization of drug components in Ginkgo Dipyridolum Injection, reduce the accumulation of toxic components in the body, and exhibit synergistic mechanisms with the two drugs, leading to increased efficacy and reduced toxicity. Therefore, there are fewer adverse reactions after administration^[11].

5. Conclusion

In summary, Epalrestat can be used as a commonly employed adjuvant drug for diabetic complications, exhibiting good efficacy. It can assist in controlling blood glucose, reduce the body's oxidative stress response, and possess high drug safety, highlighting its significant therapeutic advantages.

Disclosure statement

The authors declare no conflict of interest.

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