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ORIGINAL ARTICLE

ULTRASOUND CARDIOGRAPHY EVALUATION OF THE THERAPEUTIC EFFECTS OF GAMMA GLOBULIN IN COMBINATION WITH A GLUCOCORTICOID IN SEVERE MYOCARDITIS IN ADULTS

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Abstract

In this study, the clinical efficacy of gamma globulin in combination with glucocorticoid therapy in severe viral myocarditis in adults was analysed using ultrasound cardiography. A total of 120 hospitalised severe viral myocarditis patients were included. They were divided into an observation group (60 cases treated with intravenous injections of gamma globulin and glucocorticoid based on routine therapy) and a control group (60 cases treated with glucocorticoid based on routine therapy). The mortality, cure and relapse rates of both groups were analysed. Ultrasound cardiography was used to evaluate the changes in cardiac function in combination with myocardial enzyme evaluation before and after treatment. Healing rates in the observation group were significantly higher than in the control group. After therapy, cardiac troponin T (cTnT), creatine kinase MB (CK-MB), brain natriuretic peptide (BNP), casein kinase (CK) and lactate dehydrogenase (LDH) levels were significantly higher in the observation group than in the control group (p < 0.05). The overall response rate in the observation group (p < 0.33%) was significantly higher than in the control group (p < 0.05). Ultrasonocardiography had a very high value in the diagnosis of myocarditis. Gammaglobulin combined with glucocorticoid therapy was effective in the treatment of severe myocarditis.

Rezumat

Studiul a analizat eficacitatea clinică a gama-globulinei în combinație cu terapia cu glucocorticoizi în miocardita virală severă la adulți, utilizând cardiografia cu ultrasunete. Au fost incluși în total 120 de pacienți spitalizați cu miocardită virală severă. Aceștia au fost împărțiți într-un grup de observație (60 de cazuri tratate cu injecții intravenoase de gamma-globulină și glucocorticoid pe baza terapiei de primă linie) și un grup de control (60 de cazuri tratate cu glucocorticoid pe baza terapiei de primă linie). Au fost analizate ratele de mortalitate, vindecarea și recăderea pentru ambelor grupuri. Cardiografia cu ultrasunete a fost utilizată pentru a evalua modificările funcției cardiace în combinație cu evaluarea enzimelor miocardice înainte și după tratament. Ratele de vindecare în grupul de observație au fost semnificativ mai mari decât în grupul de control. După terapie, nivelurile troponinei cardiace T (cTnT), creatin-kinazei MB (CK-MB), peptidei natriuretice cerebrale (BNP), cazein-kinazei (CK) și lactat dehidrogenazei (LDH) au fost semnificativ mai mari în grupul de observație decât în grupul de control (p < 0,05). Rata globală de răspuns în grupul de observație (98,33%) a fost semnificativ mai mare decât în grupul de control (88,33%) (p < 0,05). Ultrasonocardiografia a avut o valoare semnificativă în diagnosticul miocarditei. Gamma-globulina combinată cu terapia cu glucocorticoizi a fost eficace în tratamentul miocarditei severe.

Keywords: gamma globulin, glucocorticoid, severe myocarditis, ultrasonocardiography

Introduction

Myocarditis is a local or diffuse inflammation of the heart muscle resulting from necrosis of cardiomyocytes due to pathogenic microbial infection or physical and chemical factors [1, 2]. Viral myocarditis is a common condition in clinical practice. A large number of patients with viral myocarditis present with a respiratory infection at an early stage. During treatment, viral myocarditis rapidly becomes severe [2]. The degree of myocardial damage varies with myocarditis severity. People with mild myocarditis have no symptoms, while those with severe myocarditis can cause heart failure and death [4]. Myocarditis affects people of all ages, especially young and middle-aged people. Viral infections are the most common cause [5, 6]. Severe myocarditis develops rapidly and has a high

mortality rate of 48% [7, 8], accounting for 30 - 40% of myocarditis cases. Arrhythmias, palpitations, syncope, heart failure and respiratory failure are the main clinical symptoms of severe myocarditis. In severe cases, patients may experience cardiogenic shock. Myocarditis involving the pericardium and pleura causes chest discomfort and pain [9]. Acute myocarditis is characterised by an acute and rapid onset, usually leading to heart failure, shock and arrhythmia. The incidence of sudden death is high. These symptoms pose significant risks to the lives of patients. Correct clinical diagnosis and management are therefore of paramount importance [10, 11]. Symptomatic treatment is a commonly used therapy for severe viral myocarditis. The use of myocardial nutritional agents, glucocorticoids and other specific treatments is still under discussion. According to relevant research, intra-aortic balloon counter-pulsation (IABP) can be used to effectively improve the success rate of rescue [12]. Extracorporeal membrane oxygenation (ECMO) also has an excellent effect [13]. Many studies have shown that gamma globulin therapy has a significant therapeutic effect on viral myocarditis. Gamma globulins have antibody-like activity and are capable of binding to antigens to form complexes. The mechanism is complex. It is widely used in the clinical treatment of immunodeficiency, immune system disorders and severe infectious diseases [14]. Glucocorticoids have anti-inflammatory, detoxifying and anti-shock effects and can improve the stability of the lysosomal membrane. However, high doses worsen the disease [15].

The detection of the disease is facilitated by a definitive clinical diagnosis based on echocardiography. In 2013, at the annual meeting of the European Society of Cardiology (ESC), criteria for the clinical diagnosis of myocarditis were proposed, including ECG accessory examination, ECG ST-T change, abnormal Q wave and supraventricular tachycardia [16]. Ultrasonocardiography could be used to detect abnormalities in cardiac structure and function. In ultrasonocardiography, the cardiograms of patients with severe myocarditis do not show features that should be determined from various aspects. The main symptoms include ventricular enlargement, abnormalities of ventricular wall motion, thickening of ventricular motion, left ventricular contraction, reduced diastolic function, atrioventricular valve regurgitation and thrombosis in the left ventricle. In some cases, hydropericardium may also be observed [17, 18]. Enhanced left ventricular myocardial echo in patients with myocarditis was demonstrated by Catena et al. [19]. Most clinical diagnosis focuses on left ventricular ejection fraction, ventricular wall motion abnormalities, degree of atrioventricular regurgitation and other single information without adequate functional assessment of cardiac structure. Evidence suggests that the level of ventricular structure, the reduction in left ventricular diastolic function and the degree of valvular damage may be associated with the outcome of heart failure in patients with severe myocarditis, suggesting that echocardiography may be able to evaluate cardiac abnormalities [20].

In this study, ultrasonocardiography was used to analyse the cardiac functions of patients with severe myocarditis. The changes in the cardiac functions of patients in two groups before and after treatment were compared to provide references for a good prognosis.

Materials and Methods

Clinical data

The following data on patients in the two groups was collected: (i) basic data (age, gender, weight, body mass index (BMI) and life behaviours); (ii) the main causes of admission, clinical symptoms, vital signs and

the time of the craniocerebral computed tomography (CT) or magnetic resonance imaging (MRI) examination; (iii) the features of carotid plaque (sites and morphology); (iv) imaging data (the analysis of imaging data on admission and postoperative skull CT plain scan); (v) medication (drug types, medication time, administration methods and dosage).

Patients

One hundred twenty patients with severe viral myocarditis treated in Deyang People's Hospital, Deyang, China, were enrolled as subjects and divided into an observation group (60 cases treated with intravenous injection of gamma globulin and glucocorticoid based on routine therapy) and a control group (60 cases treated with glucocorticoid based on routine therapy). The control group consisted of 23 men and 37 women aged between 47 and 65 years. Their mean age, mean BMI and disease progression were 40.7 ± 3.4 , $23.31 \pm 1.14 \text{ kg/m}^2$ and 5.73 ± 2.43 , respectively. The observation group consisted of 35 men and 25 women aged between 42 and 63 years. Their mean age, mean BMI and disease progression were 32.1 ± 2.7 , 23.07 ± 22.52 kg/m² and 5.36 ± 2.36 , respectively. There were no significant differences in gender, age or disease progression between the two groups. However, baseline characteristics were comparable. Vital signs were stable in patients in both groups, with no apparent contraindications for the treatment. All patients who met the inclusion criteria accepted the experimental rules and signed an informed consent form. The study was approved by the Deyang People's Hospital Ethics Committee.

In the setting of inclusion criteria, the study enrolled patients possessing comprehensive datasets. Additionally, patients exhibiting symptoms such as nausea, vomiting, fever and other clinical manifestations were considered. Those with early upper respiratory tract infections and diarrhoea, as well as those meeting clinical criteria for severe myocarditis, were included. Furthermore, individuals without an allergic predisposition to contrast and those presenting various types of premature beats and tachycardia were incorporated into the study cohort. Conversely, exclusion criteria comprised patients diagnosed with severe liver and kidney diseases. Individuals in states of coma or congestive heart failure, those afflicted with mental disorders, and individuals undergoing pregnancy or lactation were excluded from participation. Moreover, individuals experiencing mental overload preceding an ultrasound examination were also excluded from the study.

Echocardiography

The films of all subjects were reviewed in a double-blind manner by two radiologists. Any disagreement was resolved, and a consensus diagnosis was reached through image analysis by a third physician. The ultrasound cardiogram was used and was equipped with frequency conversion probes (S1 - 5 and S4) with a frequency of 2.5 MHz or 5.0 MHz (Philips IE33 ultrasound device, Philips, Netherlands). It was also

equipped with an ECG monitoring lead and an automatic image storage device. Subjects were instructed to maintain a horizontal and left-lateral position during the examination. Patients with severe myocarditis could assume a semi-reclining position. Their cardiac functions were then measured using the bi-plane method of the cross-sectional echocardiogram. Pulse Doppler bicuspid valve and pulmonary venous flow spectra were used to assess cardiac diastolic function (ATLHDI3500 colour Doppler ultrasound, ATL Company, USA).

In addition, the maximum tricuspid regurgitation velocity was measured using Doppler technology and then converted to differential pressure. The estimated right atrial pressure was then applied. During the examination, the parasternal left ventricular long-axis view, left ventricular short-axis view, bicuspid valve, aortic valve short-axis view, apical four-chamber view, apical horizontal view, papillary muscles, two-chamber view and three-chamber view were displayed. The systolic and diastolic functions of the heart and the maximum systolic pressure of the pulmonary artery were also observed. The recorded images of each procedure were stored, and the abnormalities in the cardiac functions of each subject were recorded. Biochemical indicators of cardiac function and markers of myocardial injury were determined at baseline and during treatment, including changes in lactate dehydrogenase (LDH), brain natriuretic peptide (BNP), casein kinase (CK) and creatine kinase-MB (CK-MB). Blood tests were performed using ELISA kits according to the manufacturer's specifications (Wuhan Fine Biotech Co., Ltd., China).

Treatment methods

The conventional treatment method was implemented as follows: patients were intravenously injected with 40 mg of milkvetch root (Astragalus species, Fabaceae) injection (Zhengda Qingbao Pharmaceutical Co., Ltd., China) each day. Besides, dobutamine (Yangzhou Aosaikang Pharmaceutical Co., Ltd., China) was continuously pumped intravenously (the speed of drip was 2.5 - 10 µg/kg bw per min). The rate of medication could be adjusted according to the change in blood pressure; 0.1 g of Vitamin C (VC) (Northeast Pharmaceutical Group Shenyang First Pharmaceutical Co., Ltd., China) and 10 mg of Vitamin B1 (VB1) (Northeast Pharmaceutical Group Shenyang First Pharmaceutical Co., Ltd., China) were orally taken three times each day. After that, 20 mg of trimetazidine (Jiangsu Wuzhong Pharmaceutical Group Co., Ltd., China) was taken three times per day. A diuretic drug (torasemide tablets, Nanjing Xingang United Pharmaceutical Co., Ltd., China) was used for the symptomatic treatment of different levels of heart rate, including installing a temporary pacemaker. During the treatment, bacterial or viral infections, arrhythmia and heart failure were treated with corresponding therapies. Continuous positive airway pressure was

employed for adjuvant respiration in patients with oxygen saturation and difficulty in oxygen inhalation for 1 month. A dose of 20 mg of gammaglobulin (Shanxi Kangbao Biological Product Co., Ltd., China) was intravenously dripped slowly once each day for the patients in the observational group. Glucocorticoid was used once every day. A dose of 10 mg of dexamethasone sodium phosphate (Shandong Yikang Pharmaceutical Co., Ltd., China) was intravenously administrated. *Observation indicators*

Cardiac structure, disease changes, myocardial damage changes in biochemical indicators for cardiac functions among patients in the two groups were analysed. Ultrasonocardiography (Philips IE33, Philips, the Netherlands) was utilised to detect the changes in cardiac functions in patients in the two groups before and after treatment, and the evaluation of the therapeutic effects was compared.

Effective cases: clinical symptoms generally disappeared, the myocardial enzyme spectrum was within the normal range and the ECG came back to normal.

Valid cases: clinical symptoms apparently improved, the myocardial enzyme spectrum was remarkably reduced and the ECG showed left ventricular contraction. Invalid cases: the myocardial enzyme spectrum continuously increased and clinical symptoms and ECG examination showed no obvious changes.

The total effective rate was computed as a percentage by summing the number of effective cases and valid cases and dividing this sum by the total number of cases. This was expressed using the formula:

total effective rate =
$$\frac{effective\ cases + valid\ cases}{total\ cases} \times 100\%.$$

To assess the impact of treatment, comparisons were made regarding the levels of cardiac troponin T (cTnT), CK-MB and B-type natriuretic peptide (BNP) in patients from two distinct groups before and after the therapeutic intervention.

Statistical methods

The basic data and clinical symptoms of the subjects were statistically analysed based on descriptive statistical analysis and a t-test using SPSS 22.0 (IBM, USA). Measurement data were denoted by mean \pm standard deviation (x \pm s). Enumeration data were analysed using the χ^2 test and denoted by percentages (%). A value of p < 0.05 suggested remarkable statistical differences. To reduce errors and improve the accuracy of the research, the clinical data of all subjects was measured three times. Finally, the average values were calculated. The test level was set at 0.05 and p < 0.05 demonstrated statistical significance.

Results and Discussion

Echocardiographic findings

The results of the symptoms among 120 patients in ultrasound cardiograms are presented in Table I. The abnormal rates of arrhythmia, myocardial echo abnormality,

myocardial thickening, abnormality of ventricular wall motion, cardiac chamber dilatation, cardiac function deterioration and pericarditis with hydropericardium

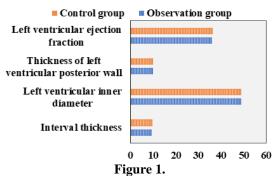
amounted to 93.33%, 92.5%, 87.5%, 89.17%, 29.17%, 35.0% and 47.5%, respectively

Table I Symptoms in ultrasound cardiograms

Symptoms	Positive	Negative	Abnormal rate
Myocardial echo abnormality	111	9	92.5%
Arrhythmia	112	8	93.33%
Myocardial thickening	105	15	87.5%
Abnormality of ventricular wall motion	107	13	89.17%
Cardiac chamber dilatation	35	85	29.17%
Cardiac function deterioration	42	78	35%
Pericarditis with hydropericardium	57	63	47.5%

Comparison of ultrasound examination indicators between two groups

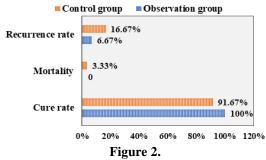
The pre-treatment ultrasound indicators of patients in the two groups were comparable, mainly including interval thickness, left ventricular internal diameter, left ventricular posterior wall thickness and left ejection fraction (p > 0.05) (Figure 1).



Comparison of ultrasound indicators between two groups

Comparison of cure rate, mortality and recurrence rate among patients between the two groups

The cure rate, mortality and recurrence rate of observation and control groups amounted to 100% (60 cases) *versus* 91.67% (55 cases), 0% (no case) *versus* 3.33% (2 cases) and 6.67% (4 cases) *versus* 16.67% (10 cases), respectively. The cure rate of the observation group was superior to that of the control group (Figure 2).



Comparison of cure rate, mortality and recurrence rate among patients between two groups

Comparison of different indicators before and after treatment

According to the comparison of the indicators for patients in the two groups before and after treatment, cTnT, CK-MB and BNP of the observation and control groups before treatment amounted to 9.21 \pm 0.21 ng/mL versus 8.32 \pm 0.21 ng/mL, 80.43 \pm 15.23 ng/mL versus 79.26 \pm 14.31 ng/mL and 1987.3 \pm 315.23 pg/mL versus 1897.3 \pm 321.31 pg/mL, respectively, before treatment. After treatment, cTnT, CK-MB and BNP of observation and control groups amounted to 0.21 \pm 0.18 ng/mL versus 0.89 \pm 0.32 ng/mL, 5.72 \pm 1.06 ng/mL versus 12.43 \pm 0.52 ng/mL and 238.72 \pm 67.23 pg/mL versus 398.87 \pm 61.35 pg/mL, respectively (Figure 3).

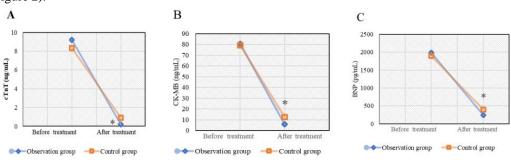
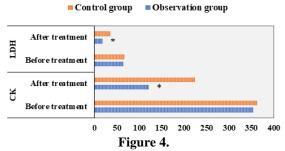


Figure 3.

Comparison of different indicators for patients in two groups before and after treatment. (**A**): Comparison of cTnT; (**B**): Comparison of CK-MB; (**C**): Comparison of BNP * Compared with the control group, p < 0.05

After treatment, the above indicators of the latter group were markedly superior to those of the former group (p < 0.05).

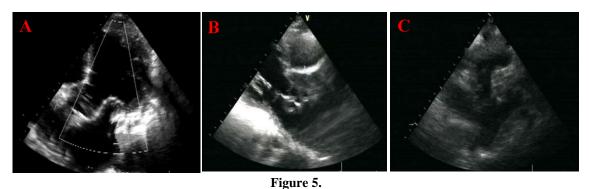


Comparison of CK and LDH between two groups * Compared with control group, p < 0.05

Comparison of CK and LDH between two groups Before treatment, no notable difference was detected in CK and LDH between the two groups. After treatment, CK and LDH in the observation and control groups amounted to 121.76 ± 18.67 U/L *versus* 224.64 ± 27.53 U/L and 18.03 ± 1.21 U/L *versus* 36.31 ± 2.06 U/L, respectively. CK and LDH levels after treatment showed a significant decrease in the observation group compared with the control group (p < 0.05) (Figure 4).

Ultrasound cardiograms

Figure 5 shows the ultrasound cardiogram of a male patient aged 53. Atrioventricular valve regurgitation, heterogeneous internal echo, left ventricular wall thickening, ventricular dilatation and ventricular reconstruction are shown in Figure 5A. Left ventricular thrombosis at the left ventricular apex is presented in Figure 5B. Hydropericardium and reduced cardiac function are displayed in Figure 5C.



Ultrasound cardiograms of case 1

(A): Obvious dilatation of the apical four-chamber view of the left ventricle; (B): Left ventricular thrombosis; (C): Nonstandard section of the apical two-chamber view and left ventricular hydropericardium

Figure 6 shows the ultrasound cardiogram of a male patient aged 57. Figure 6A showed that the papillary muscle was horizontal to the left ventricular short axis and that the left ventricular wall thickened. Deteriorated left ventricular systolic function and abnormal ventricular wall motion are displayed in Figure 6B. Myocardial

damage, left ventricular systolic and diastolic dysfunction, and increasing left ventricular end-diastolic pressure were observed in Figure 6C. Pulmonary artery systolic pressure could be estimated through bicuspid valve regurgitation differential pressure.

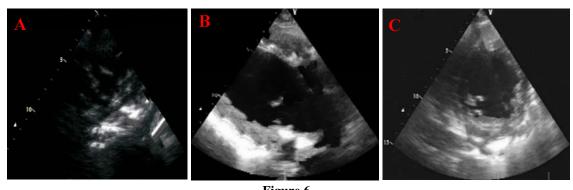
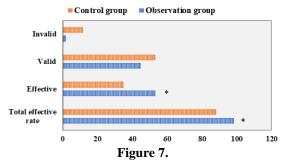


Figure 6. Ultrasound cardiograms of case 2

(A): Left ventricular wall thickening; (B): Abnormality of left ventricular cardiac function; (C): Left ventricular systolic and diastolic dysfunctions

Comparison of the total effective rate between two groups

In the observation group, there were 32 effective cases (53.33%), 27 valid cases (45.00%) and 1 invalid case (1.67%). In the control group, there were 21 effective cases (35.00%), 32 valid cases (53.33%) and 7 invalid cases (11.67%). The total effective rate in the observation group was significantly increased (98.33%) compared with the control group (88.33%) (p < 0.05) (Figure 7).



Comparison of the total effective rate between two groups

* Compared with the control group, p < 0.05

The results showed that cTnT, CK, CK-MB and BNP in the observation group were significantly higher than those in the control group (p < 0.05). The cure and mortality rates in the observation group were 100% and 0%, respectively, and the relapse rates were significantly lower than those of the control group (p < 0.05). The above research results showed that the combined therapy of gamma-globulin and glucocorticoid was more effective than gamma-globulin therapy alone, which was consistent with the research results of many scientists.

Glucocorticoid has anti-inflammatory, detoxifying and anti-shock effects and could improve myocardial function and block interferon synthesis to accelerate viral replication. This makes it unsuitable for the treatment of early myocarditis. In this study, gamma globulin was combined with a glucocorticoid to discuss its therapeutic effect in severe adult myocarditis. It was suggested that the therapy was very effective in fighting the virus and inflammation and reducing the damage to heart muscle cells caused by the virus. The immunological responses of the patients were modified. In patients with severe myocarditis, the use of gamma globulin in combination with glucocorticoid therapy effectively improved cardiac enzymes, the rate of recovery and the rate of relapse. Extensive previous studies have shown that the main mechanism of myocarditis treatment with gamma globulin is that cardiomyoviruses in the patient's body are rapidly eliminated by numerous antibodies, preventing damage to heart muscle cells. Once the immune system was stable, it was inhibited. In addition, the reduction of inflammatory cytokines was effectively improved, and

the negative inotropic effect was inhibited in patients with myocarditis. Based on the above mechanism, the stability of myocardial cell structure and function could be effectively maintained [21]. Drucker *et al.* [22] showed that a high dose of gamma globulin could improve the rehabilitation of left ventricular function and the survival rate in the first year after hospitalisation. Schauer *et al.* [23] suggested that the combined therapy of high-dose steroid and gamma globulin was safe with no apparent infections or long-term side effects. Ventricular function and survival were well rehabilitated without transplantation. Gamma globulin, in combination with glucocorticoids, was shown to have a safe and reliable therapeutic effect in severe myocarditis.

With the advent of contrast agents for ultrasound cardiography and the transesophageal probe, echocardiography has become much more sensitive and is an essential part of cardiac surgery for valve reconstruction. Echocardiography is also essential for the dynamic monitoring of severe myocarditis. After the clinical features have been established, echocardiography is performed to fully understand the cardiac structure and hemodynamic changes to improve the diagnostic efficiency of myocarditis. The clinical diagnosis of myocarditis is mainly based on the patient's chief complaint, ECG changes and elevation of serum cardiac enzymes. In patients with acute myocarditis, myocardial enzymes return to normal immediately after an increase, whereas in patients with coughs, there are still conscious symptoms.

However, the echocardiograms showed that the abnormal myocardial changes lasted for a long time, and the systolic motion was abnormal and returned to normal 1 to 1.5 months after treatment. The echocardiographic results improved as the disease progressed. Ventricular septal abnormalities generally returned to normal 2 - 4 months after treatment [24]. In this study, echocardiography was used to diagnose patients with severe myocarditis. The main ultrasound findings were arrhythmia, myocardial echo abnormality, myocardial thickening, ventricular wall motion abnormality and ventricular dilatation. In 90% of patients with myocarditis, hospital admission was due to arrhythmia and atrial and ventricular premature beats were the most common symptoms in the clinical diagnosis. Arrhythmia in patients with myocarditis is mainly caused by the cumulative cardiac conduction system. In this study, myocardial echo abnormalities occurred mainly in the ventricular septum, apex and papillary muscle in patients with severe acute myocarditis.

During the convalescent period, myocardial cell fibrosis occurred, and local or diffuse echoes were enhanced. In the acute stage of myocarditis, inflammatory cell infiltration and interstitial oedema occurred, and myocardial echo was attenuated. With regard to changes in ventricular wall thickness, myocardial matrix oedema thickneed. The main changes included thickening of

the ventricular septum or left ventricular posterior wall and reduction of echo and motion, followed by myocardial fibrosis, intimal echo enhancement and local motion reduction in the late stage. It was previously shown that abnormalities of the left coronary artery diagnosed by ultrasound cardiograms were labelled as endocardial thickening caused by endocardial fibroelastosis and excessive proliferation of fibrous and elastic tissue [25]. In this study, ultrasound techniques were used to evaluate the clinical symptoms of patients with severe myocarditis. Correct localization during surgery was essential. If the images were not clear, the scanning angle of the probe should be carefully adjusted to the correct position by slowly moving it up and down. Observation of the cardiograms should determine whether there is a ventricular septal abnormality. Increasing the dwell time is possible in such cases. The duration of dynamic echocardiography was long, especially if the echo was abnormal. Depending on the abnormalities seen on the echocardiograms, the clinicians received results confirming the diagnosis of myocarditis.

Conclusions

Ultrasound, in combination with clinical symptoms, was found to be an effective diagnostic method for myocarditis. Gamma globulin combined with glucocorticoids therapy was more effective than gamma globulin alone in the treatment of myocarditis. In patients with severe myocarditis, the combined therapy effectively improved the myocardial enzyme spectrum and the cure rate and reduced the recurrence rate. Significant therapeutic effects of traditional Chinese medicines on myocarditis were demonstrated by the data collected. In order to provide more guidance for clinical diagnosis and treatment, follow-up research should investigate the therapeutic effect of the combination of ultrasonocardiography and traditional Chinese drug therapy on myocarditis.

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