https://doi.org/10.31925/farmacia.2022.6.17 **ORIGINAL ARTICLE**

EFFECTS OF DIFFERENT DOSES OF NITROGLYCERIN COMBINED WITH ATENOLOL ON PLASMA VISCOSITY AND INFLAMMATORY RESPONSE IN PATIENTS WITH ANGINA PECTORIS

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Abstract

In order to analyse the clinical efficacy and safety of high-dose nitroglycerin combined with atenolol in patients with angina pectoris, 120 patients were randomly divided into an experimental group (n = 60) and a control group (n = 60). The patients in the experimental group received high-dose nitroglycerin (0.5 mg nitroglycerin, three times a day, for 30 consecutive days) plus atenolol (6.25 mg twice a day) while the patients in the control group received low-dose nitroglycerin (0.2 mg nitroglycerin, three times a day, for 30 consecutive days) + atenolol (6.25 mg twice a day). The results showed that the left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) in the experimental group were significantly lower than those in the control group. The levels of TNF-α, IL-6 and plasma viscosity in the experimental group were significantly lower than those in the control group. The overall clinical response rate of the experimental group (90%) was significantly higher than that of the control group (71.67%). The incidence of adverse reactions in the experimental group (8.33%) was not significantly different from that in the control group (10%), indicating that high-dose nitroglycerin combined with atenolol could effectively reduce the serum inflammatory factor level and plasma viscosity in patients with angina pectoris compared with low-dose nitroglycerin, and the therapeutic effect on patients was more significant, without increasing adverse drug reactions, with high clinical safety.

Rezumat

Pentru a analiza eficacitatea clinică și siguranța nitroglicerinei în doză mare combinată cu atenolol la pacienții cu angină pectorală, 120 de pacienți au fost împărțiți aleatoriu într-un grup experimental (n = 60) și un grup control (n = 60). Pacienții din grupul experimental au primit nitroglicerină în doză mare (0,5 mg nitroglicerină, de trei ori pe zi, timp de 30 de zile consecutiv) plus atenolol (6,25 mg de două ori pe zi), în timp ce pacienții din grupul control au primit doze mici nitroglicerină (0,2 mg nitroglicerină, de trei ori pe zi, timp de 30 de zile consecutiv) + atenolol (6,25 mg de două ori pe zi). Rezultatele au arătat că diametrul și fracția de ejecție a ventriculului stâng în grupul experimental au fost semnificativ mai mici decât cele din grupul de control. Nivelurile de TNF-α, IL-6 și vâscozitatea plasmei în grupul experimental au fost semnificativ mai mici decât cele din grupul de control. Rata generală de răspuns clinic a grupului experimental (90%) a fost semnificativ mai mare decât cea a grupului control (71,67%). Incidența reacțiilor adverse în grupul experimental (8,33%) nu a fost semnificativ diferită față de cea din grupul control (10%), ceea ce indică faptul că nitroglicerina în doză mare combinată cu atenolol ar putea reduce nivelul factorului inflamator seric și vâscozitatea plasmatică la pacienții cu angină pectorală comparativ cu nitroglicerină în doză mică, cu efecte terapeutice mai însemnate și siguranță clinică ridicată.

Keywords: nitroglycerin, atenolol, angina pectoris, left ventricular ejection fraction, plasma viscosity, inflammatory factors

Introduction

Cardiovascular disease is a major public health problem threatening the life and health adult population, resulting in 4 million deaths each year, accounting for more than 40% of total deaths, being an important cause of disability [1, 2]. In recent years, β-blockers have been widely used in the treatment of cardiovascular diseases and have become the first-line and basic drugs for a variety of cardiovascular diseases, including coronary heart disease, heart failure, tachyarrhythmia, hypertension and other diseases [3-5]. Coronary heart disease refers to heart disease caused by myocardial ischemia, hypoxia, or necrosis due to luminal narrowing or occlusion by coronary atherosclerosis, which is classified as ischemic heart disease and is the most common type of organ disease caused by atherosclerosis. Coronary heart disease is a common and frequently-occurring disease in middle and elderly people, which seriously endangers human life [6]. Most people usually have no symptoms, but there are often signs of myocardial ischemia, such as feeling precordial discomfort, or fatigue symptoms, although the symptoms are very mild, but if ECG examination is performed in time, myocardial ischemia will be found and can be prevented as soon as possible. Most of these are latent coronary heart diseases [7, 8].

Some patients have obvious symptoms, often appear retrosternal or left heart pain, mostly transient, short duration, if the acute attack is precordial severe pain, sweating, lips cyanosis and other symptoms, it indicates myocardial infarction, and it should be treated by emergency treatment before rescue by the hospital. Angina pectoris is caused by coronary insufficiency, acute temporary myocardial ischemia and hypoxia, and is an important symptom of coronary heart disease [9].

Nitroglycerin is mainly used as a simple explosive and a cardiovascular drug. Nitroglycerin can release nitric oxide, which, like endothelial relaxing factor, can activate guanylate and cyclase to increase cyclic guanylate in smooth muscle and other tissues, resulting in dephosphorylation of g-globulin light chain, regulating smooth muscle contraction to cause vasodilatation, and can play a role in dilating coronary arteries and peripheral vessels [10-12]. β-blockers are drugs that selectively bind to beta-adrenoceptors, thereby antagonizing the agonistic effects of neurotransmitters and catecholamines on β-receptors. Currently, commonly used β-blockers in clinical practice include metoprolol, bisoprolol, atenolol, propranolol, labetalol, arotinolol and carvedilol [13]. Among them, atenolol is a selective β1 adrenoceptor blocker indicated for moderate and mild hypertension due to various causes, often used for hypertension, angina pectoris, myocardial infarction, arrhythmia and hyperthyroidism, and can also be used for pheochromocytoma and glaucoma [14, 15]. Clinical studies have shown that atenolol does not aggravate hypoglycaemic reactions, induce hypertensive crisis, impair peripheral circulation, or worsen airway function in patients with obstructive airway disease like non-selective β adrenoceptor blockers when administered in small doses [16]. However, atenolol can also decrease airway function in patients with asthma or chronic obstructive pulmonary disease when administered in large doses. Therefore, the selection of the atenolol dose still needs to be clarified [17, 18].

In summary, there are many drugs for the clinical treatment of angina pectoris, and the selection of a scientific and efficient drug combination regimen is currently a problem that needs to be solved. Therefore, 120 patients with angina pectoris were randomly divided into an experimental group (n = 60) and a control group (n = 60) according to different treatment methods. The experimental group was given high-dose nitroglycerin + atenolol, while the control group was given low-dose nitro-glycerin + atenolol. The general data, cardiac function index, plasma viscosity, inflammatory response index, clinical efficacy and adverse events were compared between the two groups to deeply investigate the clinical efficacy and safety of low-dose nitroglycerin + atenolol in patients with angina pectoris.

Materials and Methods

Study subjects

A total of 120 patients with angina pectoris admitted to The Third People's hospital of Haikou City, Haikou, Hainan, China from October 2020 to February 2022 were selected as the study subjects. The study was approved by the Ethical Committee of the hospital, and the family members or patients signed the informed consent form for participation in the study.

Inclusion criteria: (1) patients diagnosed with angina pectoris by digital subtraction angiography (DSA); (2) patients with stable vital signs and no dyspnoea; (3) patients with perfect clinical data; (4) patients who are conscious and able to communicate normally; (5) patients over 18 years of age.

Exclusion criteria: (1) patients combined with acute coronary syndrome; (2) patients combined with severe liver and kidney organic disease; (3) patients taking immunosuppressive agents recently; (4) patients with drug allergy.

Treatment method

According to different treatment methods, the patients were randomly divided into the experimental group and the control group, with 60 patients in each group. The experimental group received high-dose nitro-glycerin (oral 0.5 mg nitroglycerin, three times a day, for 30 consecutive days) (Hebei Changshan Biochemical Pharmaceutical Co., Ltd., China) + atenolol (6.25 mg twice daily) (Hebei Changshan Bio-chemical Pharmaceutical Co., Ltd., China), while the control group received low-dose nitroglycerin (0.2 mg nitroglycerin, three times a day for 30 consecutive days) + atenolol (6.25 mg twice daily).

After admission, the patient was examined according to the clinical characteristics, and basic treatment measures were applied, oral 100 mg aspirin (once a day) (Hebei Changshan Biochemical Pharmaceutical Co., Ltd., China) and 70 mg clopidogrel (twice a day) (Hebei Changshan Biochemical Pharmaceutical Co., Ltd., China).

Outcome measures

General data (gender, age, body mass index (BMI), cardiac functional classification and disease duration) were recorded in both groups. Clinical efficacy evaluation criteria: markedly effective: ECG returned to normal and the frequency of angina pectoris attack decreased by more than 80%; effective: ECG basically returned to normal or ST segment increased by more than 0.05 mV after treatment, the frequency of angina pectoris attack decreased by 50% ~ 80%; ineffective: it did not meet the above criteria.

$$Total\ effective\ rate = \frac{\text{Remarkable} + Effective}{\text{Total number of cases}} \times 100\%.$$

Plasma viscosity was measured by the capillary method in both groups. Serum endothelial function (endothelin (ET), nitric oxide (NO)) and serum inflammatory factors (tumour necrosis factor (TNF-α), interleukin-6

(IL-6)) were measured by the automatic biochemical analyser (Unicel DXH 800; Beckman. Coulter, USA). Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) were measured by echocardiography before and after treatment. Adverse events (headache, hypotension, nausea) were followed up and recorded in both groups, and the incidence of adverse reactions was calculated.

Statistical methods

Data were statistically analysed using SPSS 22.0 software (IBM, NY, USA). Test level $p < 0.05$. Measurement data: normally distributed data: means ± standard deviation was used for statistical description and *t* test was used for statistical inference; not normally distributed data: medians ± interquartile ranges were used for statistical description and rank sum test was used for statistical inference.

Enumeration data: Frequency and percentage were used for statistical description, and chi-square test was used for statistical inference.

Results and Discussion

Comparison of clinical data

In the experimental group there were 31 males and 19 females with an average age of 53.39 ± 6.14 years and body mass index (BMI) of 24.41 ± 1.05 (Figure 1). According to coronary heart disease stage, there were 25 cases grade I, 23 cases grade II and 12 cases grade III in the experimental group (Figure 2). In the control group there were 29 males and 21 females with an average age of 55.78 ± 8.05 years and BMI of 23.68 ± 0.84 years (Figure 1). Regarding coronary heart disease stage, there were 23 cases grade I, 21 cases grade II and 16 cases grade III in the control group (Figure 2). Among them, there was no significant difference in gender, age, BMI and coronary heart disease stage between the experimental and control groups ($p > 0.05$).

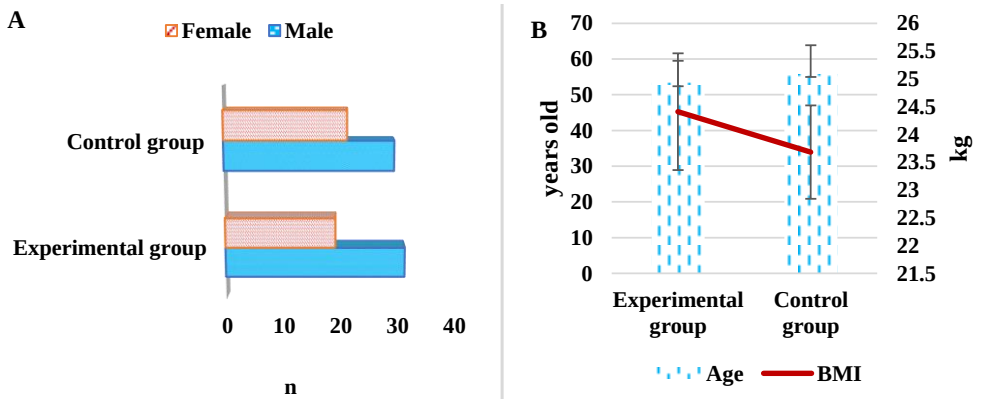

Figure 1.
Comparison of gender, age and BMI between the two groups
A is gender; B is age and BMI

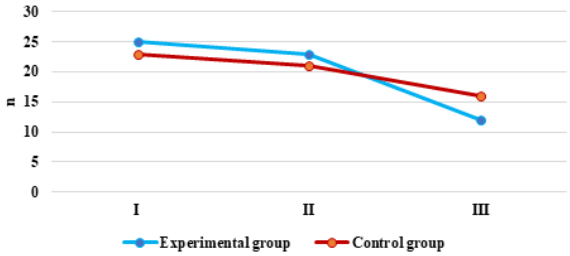

Figure 2.
Comparison of cardiac functional classification between the two groups

Comparison of cardiac function indexes before and after treatment

As shown in Figures 3 and 4, in the experimental group, the cardiac function indexes LVEDD was 64.38 ± 9.51 mm, LVESV was 64.73 ± 7.68 mL and LVEF was 42.88 ± 6.74% before treatment; LVEDD was 52.26 ± 9.79 mm, LVESV was 79.15 ± 8.04 mL and LVEF was 57.12 ± 8.31% after treatment. In the control group, before treatment, LVEDD was 64.07 ± 9.14 mm, LVESV was 64.09 ± 8.55 mL and LVEF was 43.51 ± 8.26%; after treatment, LVEDD was 57.14 ± 6.85 mm, LVESV was 71.03 ± 7.46 mL and LVEF was 49.08 ± 7.14%. Among them, the cardiac function indexes LVEDD, LVESV and LVEF of the experimental group before treatment were not significantly different from those of the control group ($p < 0.05$); the cardiac function indexes LVEDD, LVESV and LVEF of the two groups after treatment were significantly different from those before treatment ($p < 0.05$); LVEDD of the experimental group after treatment was significantly lower than that of the control group, while LVESV and LVEF were significantly higher than those of the control group ($p < 0.05$).

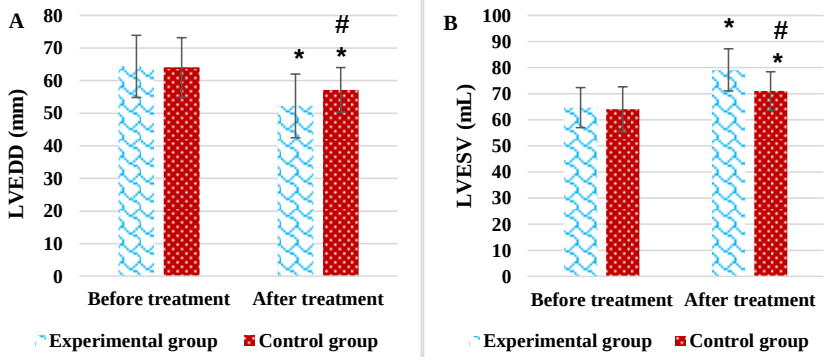

Figure 3.

Comparison of LVEDD and LVESV before and after treatment between the two groups

A: LVEDD; B: LVESV; * indicates statistically significant difference from pre-treatment ($p < 0.05$); # Compared with experimental group, $p < 0.05$)

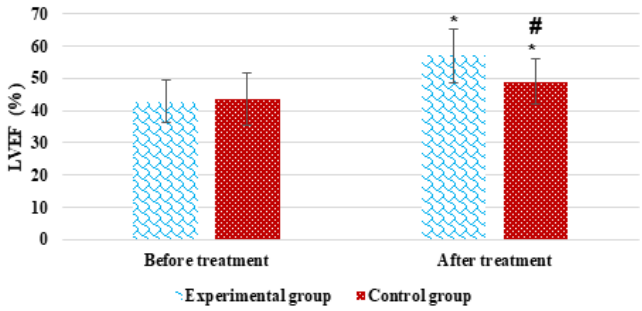

Figure 4.

Comparison of LVEF before and after treatment between the two groups

* indicates statistically significant difference from pre-treatment ($p < 0.05$); # compared with from experimental group ($p < 0.05$)

Comparison of inflammatory factor levels before and after treatment

As shown in Figures 5 and 6, in the experimental group, TNF-α was 46.73 ± 8.83 ng/L and IL-6 was 194.48 ± 15.81 ng/L before treatment; TNF-α was 46.73 ± 8.83 ng/L and IL-6 was 116.37 ± 13.07 ng/L after treatment. In the control group, TNF-α was 47.22 ± 9.27 ng/L and IL-6 was 191.09 ± 18.23 ng/L before treatment; TNF-α was 31.58 ± 3.68 ng/L and IL-6 was 142.75 ± 15.04 ng/L after treatment. Among them, TNF-α and IL-6 in the experimental group before treatment were not significantly different from those in the control group ($p > 0.05$); the levels of inflammatory cytokines TNF-α and IL-6 in the two groups after treatment were significantly lower than those before treatment ($p < 0.05$); the levels of inflammatory cytokines TNF-α and IL-6 in the experimental group after treatment were significantly lower than those in the control group ($p < 0.05$).

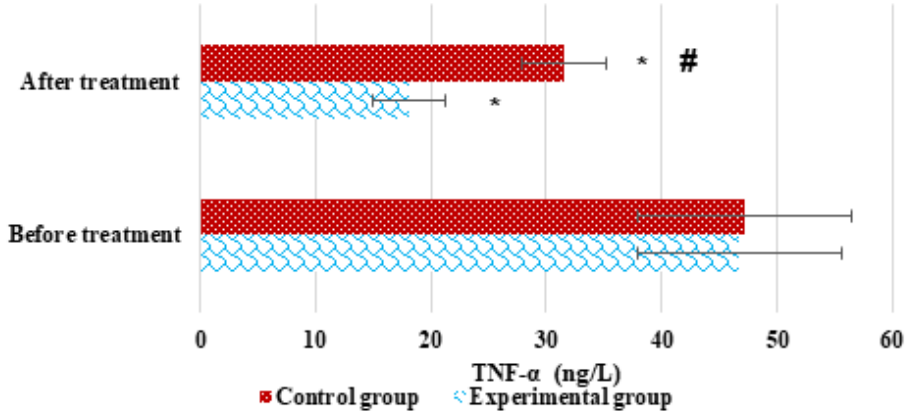

Figure 5.

Comparison of TNF-α expression before and after treatment between the two groups

* indicates statistically significant difference from pre-treatment ($p < 0.05$); # compared with from experimental group ($p < 0.05$)

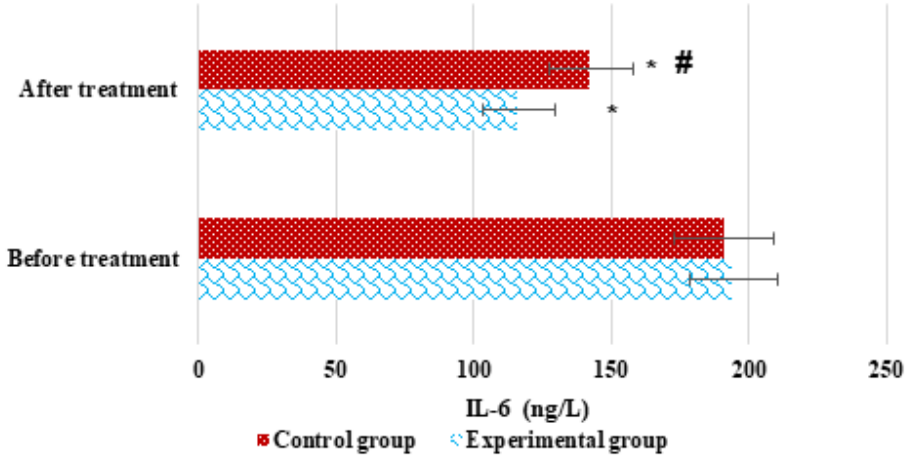

Figure 6.
Comparison of IL-6 expression before and after treatment between the two groups
* indicates statistically significant difference from pre-treatment ($p < 0.05$); # compared with experimental group ($p < 0.05$)

Comparison of plasma viscosity before and after treatment

As shown in Figure 7, the plasma viscosity of patients in the experimental group was 12.54 ± 2.64 mPa·s before treatment and 8.78 ± 2.21 mPa·s after treatment; the plasma viscosity of patients in the control group was 12.71 ± 2.57 mPa·s before treatment and 10.03 ± 1.73 mPa·s after treatment. The plasma viscosity of the experimental group before treatment was not significantly different from that of the control group ($p > 0.05$); the plasma viscosity of the two groups after treatment was significantly lower than that before treatment, and the difference was statistically significant ($p < 0.05$); the plasma viscosity of the experimental group after treatment was significantly lower than that of the control group ($p < 0.05$).

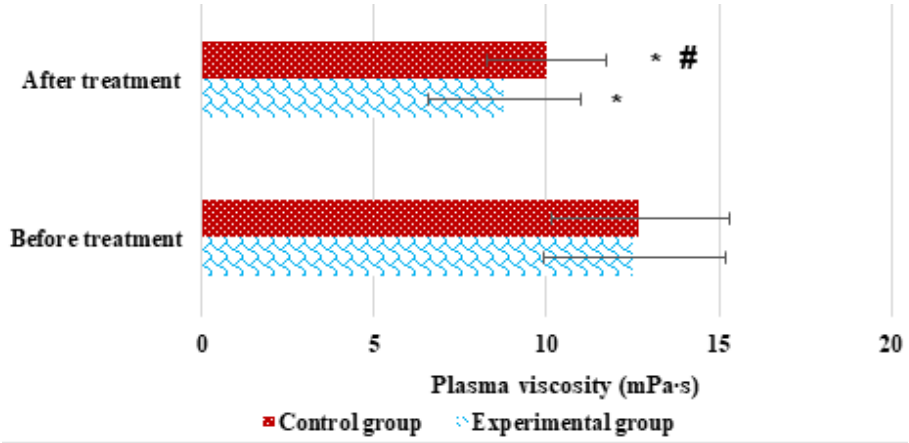

Figure 7.
Comparison of plasma viscosity before and after treatment between the two groups
* indicates statistically significant difference from pre-treatment ($p < 0.05$); # compared with experimental group ($p < 0.05$)

Comparison of clinical efficacy

As shown in Figure 8, in the experimental group, for 33 patients the treatment was significantly effective, for 21 was effective, and for 6 was ineffective. In the control group, for 25 patients the treatment was significantly effective, for 18 was effective, and for 17 was ineffective. The overall clinical response rate of the experimental group (90%) was significantly higher than that of the control group (71.67%) ($p < 0.05$).

Comparison of incidence of adverse reactions

As shown in Figure 9, there were 1 case of headache, 3 cases of hypotension and 1 case of nausea in the experimental group compared with 3 cases of headache, 1 case of hypotension and 2 cases of nausea in the control group. The incidence of adverse reactions in the experimental group (8.33%) was not significantly different from that in the control group (10%) ($p > 0.05$).

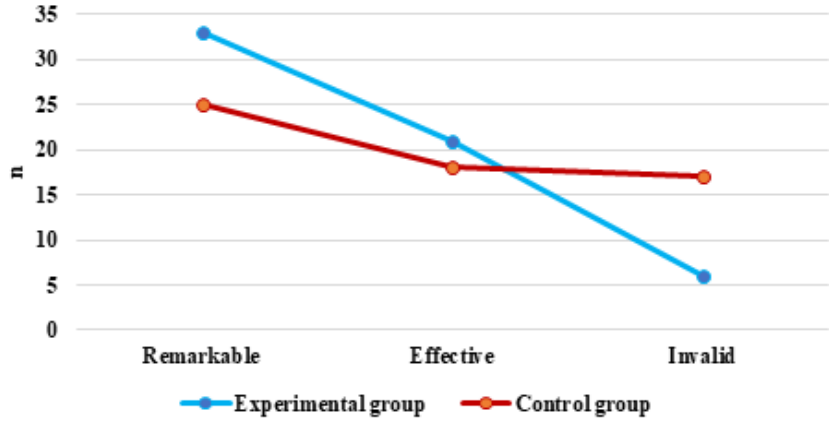

Figure 8.
Comparison of clinical efficacy between the two groups

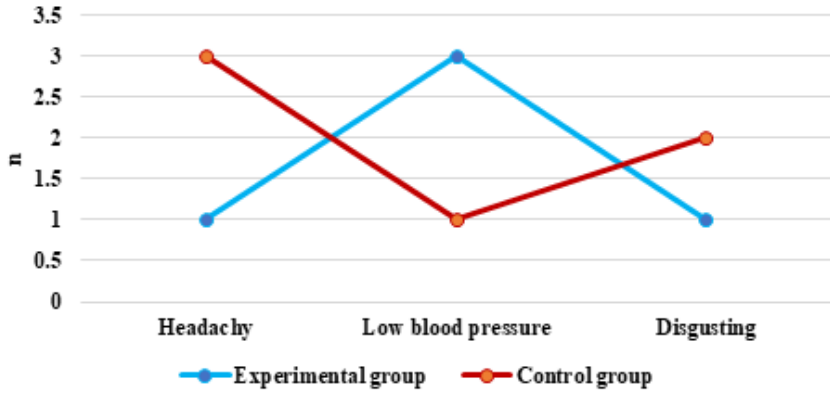

Figure 9.
Comparison of incidence of adverse reactions between the two groups

Angina pectoris is a group of syndromes caused by acute temporary myocardial ischemia and hypoxia. When patients suffering from coronary heart disease, poor myocardial blood supply and excessive metabolites (such as lactic acid) accumulate in the myocardium and can't be transported away. These products can stimulate the heart's afferent sympathetic nerve into the brain, producing pain, so angina is caused by myocardial ischemia, which is an important symptom of coronary heart disease [19-21]. Currently commonly used drugs to improve ischemia and relieve symptoms include β-blockers, nitrates, calcium channel blockers, nicorandil and trimetazidine, so it is very important to select the appropriate drug [22, 23]. A total of 120 patients with angina pectoris admitted to the hospital were selected as the study subjects. The patients were randomly divided into the experimental group (n = 60) and the control group (n = 60) according to different treatment methods. The experimental group was given high-dose nitroglycerin + atenolol, and the control group was given low-dose nitroglycerin + atenolol. From the general data, there was no significant difference in gender, age, BMI and cardiac functional classification between the experimental and control groups. The balance of baseline data between groups is to ensure the inter-group comparability of the observation results of response variables, to investigate the real effect of treatment factors on the observation results under similar baseline conditions and match the corresponding measurement methods [24]. Thus, this result provides feasibility for later studies.

LVEDD, LVESV and LVEF are all commonly used indicators to evaluate cardiac function. LVEF can reflect the functional status of the heart. LVEDD refers to the filling volume at the end of the left ventricular diastole, and its normal value is 75 ~ 160 mL. LVESV can reflect the systolic function of the left ventricle and its normal value is < 49 mL/m^2 [25, 26]. It was found that LVEDD, LVESV and LVEF in the experimental group were significantly lower than those in the control group, which indicated that high-dose nitroglycerin combined with atenolol could more effectively improve the cardiac function of patients with angina pectoris compared with low-dose nitroglycerin. From the level of inflammatory factors, the levels of inflammatory cytokines TNF-α and IL-6 in the experimental group were significantly lower than those in the control group, which indicated that high-dose nitroglycerin combined with atenolol could reduce the level of serum

inflammatory factors and relieve the inflammatory response of the body in patients with angina pectoris.

Plasma viscosity is one of the important factors affecting whole blood viscosity. The whole blood viscosity must increase when the plasma viscosity increases, which mainly depends on the concentration of plasma proteins, especially fibrinogen, lipoprotein and globulin. It is one of the indicators reflecting blood fluidity [27]. It was found that the plasma viscosity of patients in the experimental group after treatment was significantly lower than that in the control group, which indicated that high-dose nitroglycerin combined with atenolol could significantly improve the plasma viscosity and improve blood fluidity in patients with angina pectoris, and the effect was better than that of low-dose nitroglycerin as similarly observed in other studies [28]. In addition, the overall clinical response rate of patients in the experimental group (90%) was significantly higher than that in the control group (71.67%), which indicated that high-dose nitroglycerin combined with atenolol had a more significant therapeutic effect on patients with angina pectoris compared with low-dose nitroglycerin. There was no significant difference in the incidence of adverse reactions between the experimental group (8.33%) and the control group (10%), which suggested that high-dose nitroglycerin combined with atenolol did not increase adverse drug reactions and had high clinical safety.

Conclusions

The results showed that compared with low-dose nitroglycerin, high-dose nitroglycerin combined with atenolol could effectively reduce the levels of serum inflammatory factors and plasma viscosity in patients with angina pectoris, with a more significant therapeutic effect on patients, without increasing adverse drug reactions and with high clinical safety. However, there are some short-comings, the selected patients are from the same hospital, there are geographical limitations, and there is no follow-up for the prognosis of patients, so it is necessary to re-include more patients with coronary heart disease later, and further elucidate the clinical application value of high-dose nitroglycerin.

In conclusion, this result provides a reference for the clinical treatment of angina pectoris.

Conflict of interest

The authors declare no conflict of interest.

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