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Improvement in hemodynamics of amlodipine besylate combined with metoprolol in patients with hypertension complicated by heart failure

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Abstract: To observe the effect of amlodipine besylate combined with metoprolol in treating hypertension and heart failure. Total number of patients with hypertension combined with HF admitted to our hospital was One hundred and fifty from May 2017 to May 2022 selected for the study and they were distributed into single drug group and combination group by the method of random number table, with the total number of 75 cases in every group. Metoprolol treatment was given to the single drug group and metoprolol combined with amlodipine besylate treatment was given to the combination group. Both groups' scientific outcomes were compared, including their ventricular function, inflammatory factors, hemodynamics and liver and kidney function. Adverse treatment-related side events for patients were also tallied. Compared to the single drug group, the combination group's overall treatment effectiveness was higher ($P<0.05$). The combined group had better ventricular function, improved hemodynamics and lower levels of inflammatory factors ($P<0.05$). The liver, kidney function and adverse effects outcomes were the same in both groups ($P>0.05$). Amlodipine besylate combined with metoprolol has a better clinical effect in treating hypertension combined with heart failure, which can more effectively improve patients' cardiac function, inflammation and hemodynamics.

Keywords: Amlodipine besylate, metoprolol, hypertension, heart failure, hemodynamics.

INTRODUCTION

Hypertension is common chronic disease internationally today, with an average of 1 in 3 adults suffering from hypertension (Lamirault *et al*., 2020). In addition, with the aggravation of the global aging problem, the incidence of hypertension is growing with time, and it is expected that the number of hypertensive patients worldwide will exceed 500 million cases by 2030 (Al Ghorani *et al*., 2022). As a painless but lifelong treatment-required disease, hypertension can cause serious malignant lesions in the cardiovascular and cerebrovascular system, endangering the life and health of patients (Alpsoy, 2020). Among these, heart failure (HF) is one of the extremely common complications of hypertension (Boulestreau *et al*., 2022). According to statistics, the number of HF cases in China reached 6.5-8.75 million in 2019 and more than 90% of these patients have hypertensive disease (Di Palo and Barone, 2020). In the case of patients with hypertension combined with HF, hypertension can make HF more difficult to treat and patients are at a significantly increased risk of poor prognosis (Slivnick and Lampert, 2019). Therefore, it is extremely important to find an effective and safe treatment for patients with hypertension combined with HF as soon as possible to protect the lives of patients.

Metoprolol (MP) is a commonly used drug in clinical practice for the treatment of hypertension combined with HF and belongs to the category of β-blockers, which can inhibit sympathetic hyperexcitability and thus achieve lower blood pressure and heart rate (Morris and Dunham, 2022). However, it was found that after prolonged use of MP, patients are prone to adverse effects such as dizziness and headache, decreased appetite and hypotension (Juraschek *et al*., 2018). Thus, there is an urgent clinical need to find a safer way to intervene. Amlodipine besylate (AB), a calcium antagonist, acts vascular smooth muscle to decrease peripheral vascular resistance in patients, achieving ideal blood pressure control in hypertensive patients (Hendriksen *et al*., 2022). But studies have also suggested that combining AB with MP can be effective in patients with adverse effects during treatment (Engeli *et al*., 2018), but more studies are lacking to confirm this.

To provide a more consistent protection assurance for patients with hypertension combined with HF, this study will start a preliminary analysis of the application effect of AB combined with MP to provide a more reliable clinical reference.

MATERIALS AND METHODS

Patient data

One hundred and fifty patients with hypertension combined with HF admitted from May 2017 to May 2022 were selected for the study, and they were distributed into a single drug group and a combined group with a random table method, with 75 cases in every group. MP treatment was given to the single drug group and MP combined with AB treatment was given to the combination group. The hospital's ethics committee approved the study (No.NK0256847) and signed all the study subjects. The two groups had no statistically significant change in the

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scientific baseline data (P>0.05, table 1).

Inclusion and exclusion criteria

Inclusion criteria: The diagnosis was confirmed according to the diagnostic guidelines for hypertension and chronic HF (Di Palo and Barone, 2022, Yin *et al*., 2022); there were no drug allergies; patients and their families were informed and agreed. Exclusion criteria: patients with unconsciousness or psychiatric diseases; patients with abnormal liver and kidney functions; patients with combined malignant neoplastic diseases; patients who died during treatment.

Methods

Patients were given routine treatment such as diuresis and nutrition after admission and were closely monitored for symptoms such as urinary retention. The single drug group was given MP (AstraZeneca Pharmaceutical Co., Ltd., H32025391) 2 times/d, 25mg/dose. After oral administration, patients' heart rate and blood pressure were observed and the dose was increased according to the actual situation of patients and the dose was doubled at 2-4 weeks and increased to 100mg/dose when maintenance treatment was given. In the combination group, AB (Pfizer Pharmaceuticals Limited, H10950224) was added to the single drug group, 1 time/d, 5 mg/dose, and the dose was increased according to the actual situation of patients and the maximum dose was less than 10 mg/dose. Eight weeks was a course of treatment, and both groups of patients were treated continuously for 3 courses.

Efficacy evaluation

Refer to the guidelines for the treatment of hypertension and HF (de Leeuw and Kroon, 1998): markedly effective: After treatment, the patient's symptoms and signs were completely relieved, diastolic blood pressure decreased >10-20 mmHg and reached normal and NYHA cardiac function improved ≥2 grade; effective: After treatment, signs and symptoms partially resolved, diastolic blood pressure decreased <10 mmHg and cardiac function improved by grade 1; ineffective: The above criteria were not met.

Total effective rate = (markedly effective + effective) / total number of patients × 100%

Outcome measures

Before and after the three therapy sessions, left ventricular end-systolic dimension (LVESd), left ventricular ejection fractions (LEVF) and left ventricular end-diastolic dimension (LVEDd) and were evaluated with the Doppler echocardiography (Philips iE33). The extra vascular lung water index (EVLWI), central venous pressure (CVP), mean arterial pressure (MAP) and heart rate (HR) were all measured using a pulse-indicator continuous cardiac output (PiCCO) monitor. Using an enzyme-linked immunosorbent assay, the levels of interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF) were determined in the patient's venous blood (ELISA). The biochemical enzymes serum creatinine, creatine kinase (CK) and alanine transaminase (ALT) were measured using an automatic biochemical analyzer (Scr). Additionally, the frequency of negative effects (including nausea, vomiting and lightheadedness) throughout patient treatment was also recorded, and this frequency was computed.

STATISTICAL ANALYSIS

Software SPSS22.0 was used to process the statistical data. The measuring data ($\bar{\chi}\pm s$) were compared using the independent sample t-test and paired t-test, while the counting data [n(%)] were compared using the chi-square test. At P<0.05, whereas difference was deemed significant.

RESULTS

The clinical efficacy of the combination group was better than that of the single-drug group

After treatment, it was seen that 57.33%, 37.33% and 5.33% of patients in the combination group were markedly effective, effective and ineffective, respectively, with a total treatment efficiency of 94.67%, while the overall treatment efficiency of one drug group was 82.67%. The total treatment efficiency was higher in the combination group than in the single drug group (P<0.05, table 2).

Cardiac function was better in the combined group than in the control group after the treatment

LVEDd and LVESd were (43.43±5.05) mm and (38.85±6.74) mm after treatment in the combined group, respectively, which were lower than before treatment, whereas LVEF was (54.44±6.20) % after treatment, which was higher than before treatment (P<0.05). Similarly, LVEDd and LVESd were even lower and LVEF was higher in the single-drug group than before treatment (P<0.05). Comparison of cardiac function after treatment between the two groups showed that LVEDd and LVESd were lower in the combined group and that LVEF was more than in the single group (P<0.05, fig. 1).

Inflammatory factors were lower in the combination group than in the control group after the treatment

After 3 courses of treatment, IL-1β, IL-6 and TNF-α were reduced to (12.05±1.79) ng/L, (38.02±4.96) ng/L and (15.84±2.00) ng/L, respectively, in the combination group, while IL-1β, IL-6 and TNF-α were reduced to (16.78±1.49) ng/L, (46.51±3.69) ng/L and (19.70±2.20) ng/L in the single drug group. Regarding inflammatory factors after treatment in both groups, the combination group was lower than the single drug group (P<0.05, fig. 2).

Table 1: Clinical baseline table

	Single drug group (n=75)	Combination group (n=75)	χ^2 (t)	P
Male	52 (69.33)	55 (73.33)	0.29	0.59
Age	65.57±6.12	67.04±5.25	1.58	0.12
Duration of hypertension (years)	5.75±2.05	5.20±1.69	1.79	0.08
Duration of HF (months)	4.13±1.55	4.48±1.32	1.49	0.14
History of cardiovascular disease			0.41	0.52
Yes	12 (16.00)	15 (20.00)		
No	63 (84.00)	60 (80.00)		
Long-term smoking			0.97	0.32
Yes	36 (48.00)	30 (40.00)		
No	39 (52.00)	45 (60.00)		

Table 2: Clinical efficacy table

Group	N	markedly effective	Effective	ineffective	total effective rate
Single drug group	75	27 (36.00)	35 (46.67)	13 (17.33)	82.67%
Combination group	75	43 (57.33)	28 (37.33)	4 (5.33)	94.67%
χ^2					5.37
P					0.02

Table 3: Table of adverse reactions

Group	N	Dizziness	Nausea and vomiting	Bradycardia	Mild rash	Lack of power	Total incidence
Single drug group	75	2 (2.67)	3 (4.00)	1 (1.33)	1 (1.33)	3 (4.00)	13.33%
Combination group	75	3 (4.00)	3 (4.00)	2 (2.67)	1 (1.33)	4 (5.33)	17.33%
χ^2							0.46
P							0.50

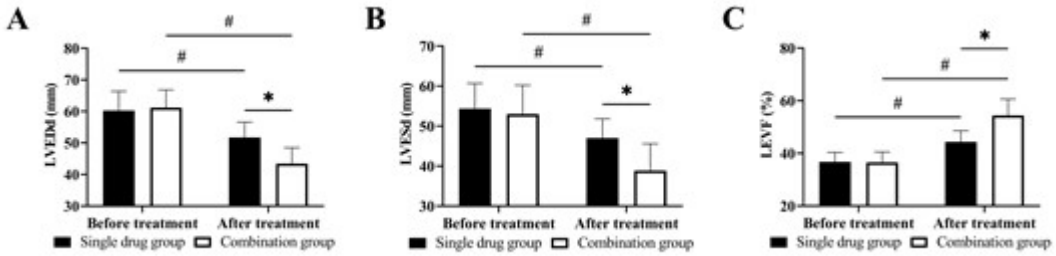

Fig. 1: Contrast of cardiac function before and after the experiment. A, B, and C are comparisons of LVEDd, LVESd and LVEF, respectively. Note: compared with pr-treatment is denoted by $^{\#}P<0.05$; compared with the group of a single drug, it is denoted by $^{*}P<0.05$,

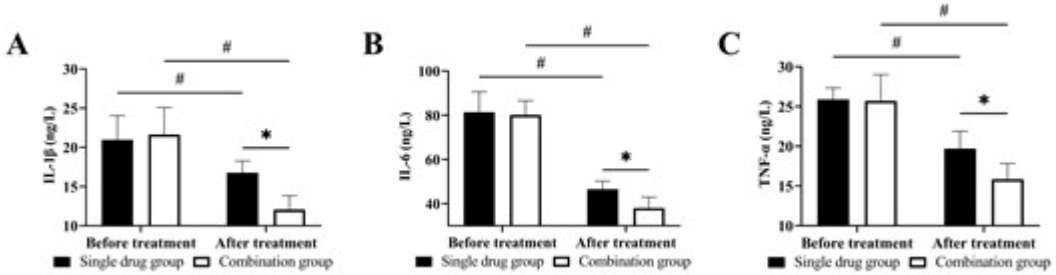

Fig. 2: Comparison of inflammatory factors before and after treatment. A, B and C are comparisons of IL-1β, IL-6 and TNF-α, respectively. Note: compared with before treatment, $^{\#}P<0.05$, compared with single drug group, $^{*}P<0.05$,

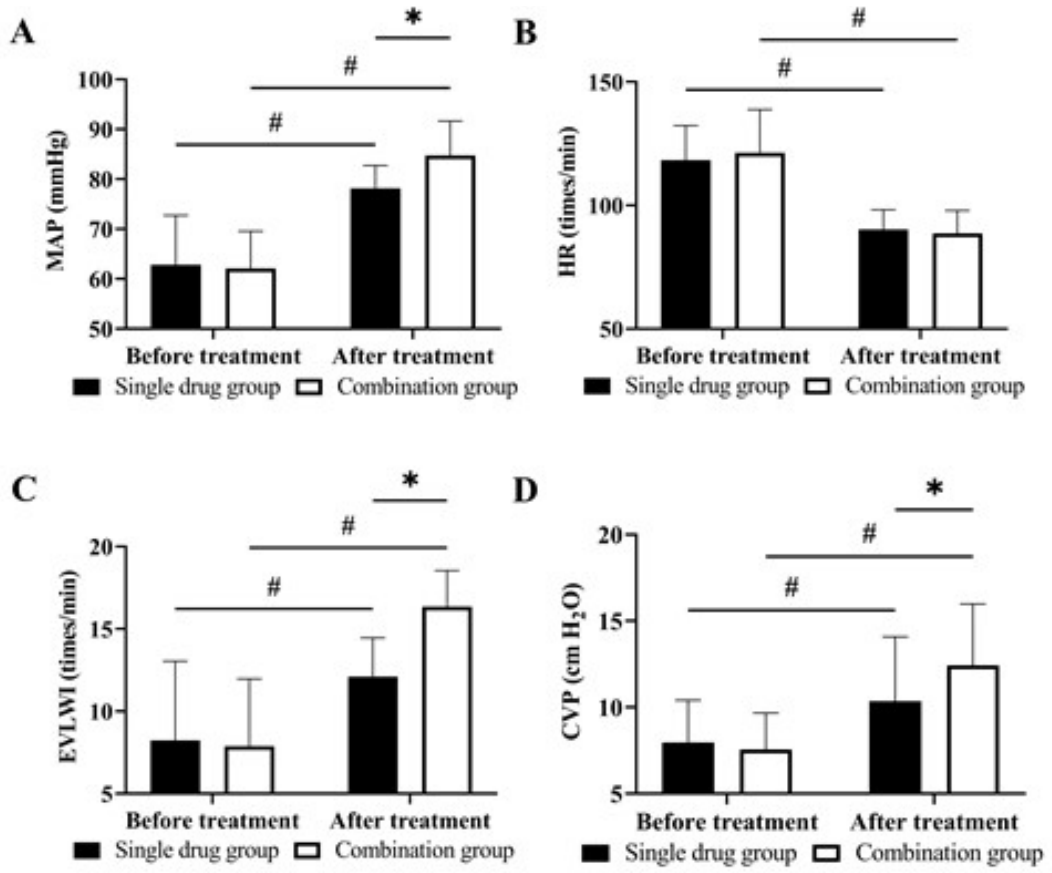

Fig. 3: Comparison of hemodynamic forces before and after treatment. A, B, C and D are comparisons of MAP, HR, EVLWI and CVP, respectively. Note: compared with pre-treatment, #P<0.05, compared with single drug group, *P<0.05,

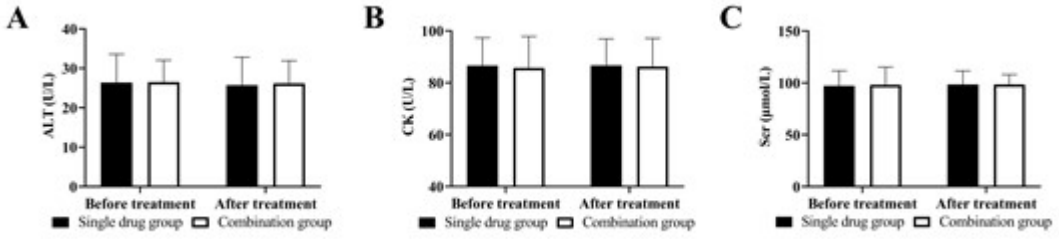

Fig. 4: Comparison of liver and kidney function before and after treatment. A, B and C are comparisons of ALT, CK and Scr, respectively.

Hemodynamics were better in the combined group than in the control group after the treatment

Before therapy, there was no significant change between the groups' hemodynamic indexes (P>0.05). Following treatment, MAP, EVLWI and CVP increased, with the combined group outperforming the control group (P<0.05). HR was lower in both groups after treatment than before treatment (P<0.05), but there was no difference between the two groups (P>0.05, fig. 3)

No difference in liver and kidney function between for two groups in post treatment

Before and after treatment, there were no differences in the results of ALT, CK and Scr assay between was groups (P>0.05) and there were also no significant changes in liver and kidney function indexes before and after treatment (P>0.05, fig. 4), indicating that the effects of both treatments on liver and kidney function were small.

No difference in adverse reactions between both groups

During treatment, adverse reactions such as dizziness, nausea and vomiting, and bradycardia were seen in both groups, of which the total incidence of adverse reactions in the combined group was 17.33%. The difference was not statistically remarkable compared with the overall occurrence of adverse responses in the control group of 13.33% (P>0.05, table 3).

DISCUSSION

It is well known that HF is a process of gradual decline in cardiac function, and the main purpose of correcting HF in clinical practice is "diuresis, vasodilation, and enhancement of cardiac function" (Jackson *et al*., 2021). Among them, MP, as a β-blocker, acts on myocardial β-receptors to slow down the heart rate, improve myocardial energy metabolism, and decrease myocardial oxygen consumption (Zaatari *et al*., 2021). But studies have also pointed out that MP can attenuate the toxic effects of catecholamines on cardiomyocytes, improve left ventricular compliance, correct abnormal Ca^{2+} transport in failing cardiomyocytes, and repair damaged myocardium, thus delaying, reversing and reducing myocardial remodeling and improving systolic and diastolic functions of cardiomyocytes (Grassi, 2018). While AB, a next-level long-acting intra-dihydropyridine calcium antagonist, has a relaxing vascular and blood pressure-lowering effect and has good efficacy in treating hypertensive disorders (Johnson *et al*., 2019). Although both drugs have now been shown to have excellent effects in combined HF in hypertension, studies combining the two have been relatively rare. Therefore, the present study has important implications for the future treatment of clinical hypertension combined with HF.

According to the results of the current study, AB mixed with MP has a more desirable effect in the treatment of hypertension combined with HF than MP alone. This was demonstrated by the fact that the combined group's overall treatment efficiency was more significant than the control group. This is also in line with the findings of earlier research (Kanorskii and Sereda, 2016), which can corroborate the results of the current experiment. We speculate this may be because AB can selectively inhibit the transmembrane proceeding Ca^{2+} in cardiomyocytes and smooth muscle cells, effectively reducing peripheral vascular resistance (Lee *et al*., 2022). Combined with MP, it can improve patients' blood pressure while protecting cardiomyocytes, making the treatment more effective (De Becker and Van de Borne, 2018). When we compared the post-treatment cardiac function in the two groups, it was also seen that LVEDd and LVESd were lower and LEVF was higher in the combined group, which could again verify that AB combined with MP had a superior improvement in cardiac function in patients with HF. What's more, in the comparison of inflammatory factors between the two groups, we also saw lower levels of IL-1β, IL-6 and TNF-α after treatment in the combination group, indicating that AB combined with MP also had a more significant inhibitory effect on the inflammation in patients with hypertension combined with HF. It is well known that IL-1β, IL-6 and TNF-α, as the most important inflammatory factors in the human body, are directly involved in the pathological damage process of HF and their elevated levels can aggravate the inflammation of the body, increase the risk of infection in patients, and have a serious harm to cardiometabolism, which in turn aggravates the condition of patients (Chennamadhavuni, *et al*., 2022). Research has shown that AB can improve the inflammation of patients by dilating small peripheral arteries and decreasing peripheral resistance, resulting in an increase in myocardial oxygenation (Ferreira, Tostes *et al*., 2021). The results of the current study are also consistent with the findings of Dikalova *et al*. (2020), which could again corroborate the effective ameliorative effect of AB combined with MP on the inflammation.

Moreover, we learned that MAP, EVLWI and CVP were higher in the combination group than in the single drug group after treatment, indicating that AB combined with MP also had a more excellent effect on patients' hemodynamics. This also suggests that AB combined with MP can more effectively improve patients' blood flow and provide cardiac blood supply capacity, which is not only important for the treatment of HF, but also can effectively prevent the occurrence of other cardiovascular diseases and pulmonary edema, providing a more reliable guarantee for their prognosis and safety. In comparing liver and kidney function, we saw no significant improvement in ALT, CK and Scr before and after treatment in both groups, which indicates that AB combined with MP also has a high safety profile and does not negatively affect the liver and kidney function of patients. Also, no difference in adverse effects was seen between the two groups in this study, which also validates the results of the above experiment. This is highly applicable to patients with HF in combination with hypertension who commonly have a combination of other underlying diseases and poor body function.

Nevertheless, as hypertension and HF are chronic diseases of long duration, we still need to follow up with patients for a longer period to assess the impact of AB combined with MP on the longstanding prognosis of patients. Meanwhile, the dosage for AB combined with MP is the focus of further research. Subsequently, we will conduct a more comprehensive study to address the above limitations as soon as possible to provide a more comprehensive clinical reference.

CONCLUSION

Amlodipine besylate combined with metoprolol has a better clinical effect in treating hypertension combined with heart failure, which can more effectively improve patients' cardiac function, inflammation, and hemodynamics. It also has a higher safety profile, which is worth popularizing clinically, thus providing a more reliable prognosis for hypertension and heart failure patients.

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