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Effect of metoprolol tartrate tablets and recombinant human B-type natriuretic peptide on the sudden cardiac death and malignant arrhythmias in patients with acute myocardial infarction and heart failure

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Abstract: To explore the effect of metoprolol tartrate tablets and recombinant human natriuretic peptide B (NPPB) on sudden cardiac death and malignant arrhythmias in patients with acute myocardial infarction and patients with heart failure (AMI-HF). A total of 105 AMI-HF patients treatedfrom January 2020 and June 2021 were enrolled and divided into Group I (n=53) and Group II (n=52). Both groups received conventional treatment, and Group II was additionally treated with metoprolol tartrate tablets and NPPB. The clinical observation indicators of the two groups of patients were compared. Group II had better left ventricular end diastolic diameter (LVEDd), left ventricular end systolic diameter (LVESD) and left ventricular ejection fraction (LVEF) (p<0.05). The standard deviation of NN (R-R) interval (SDNN), mean NN (R-R), root mean square of continuous difference (RMSSD) and the percentage of difference between adjacent RR intervals >50ms (pNN50) increased after treatment, with more increase in the Group II (p<0.05). Group II obtained significantly lower levels of B type natriuretic peptide (BNP),N terminal pro B type natriuretic peptide (NT-ProBNP), interleukin (IL)-6 and hs-CRP in contrast to Group I (p<0.05). Markedly higher total response rates were observed in Group II (p<0.05). The combination of metoprolol tartrate tablets and NPPB is effective in treating AMI-HF.

Keywords: Myocardial infarction, heart failure, metoprolol tartrate tablets, recombinant human B-type natriuretic peptide.

INTRODUCTION

Acute myocardial infarction or heart failure (AMI-HF) is attributed to a dramatic reduction or interruption of blood supply in the diseased coronary arteries, resulting in ischemic myocardial necrosis with left heart failure due to the inability of the patient's cardiac output to meet systemic demand (Vora *et al*., 2012). The disease is a pump failure with an urgent condition and a high mortality rate (Klein *et al*., 2018). Since 1980s, the widespread use of aspirin and streptokinase in clinical treatment has driven down the 35-d mortality rate of AMI patients from 13.2% to 8.0%, suggesting a high clinical application value. Previous studies have pointed out that AMI is one of the main precipitating causes of HF, which underscores the importance of the control of the myocardial infarction area and cautions to factors that precipitate or exacerbate heart failure (Song *et al*., 2017; Allam *et al*., 2016; Dadarwal *et al*., 2012). Related studies have also shown that recombinant human natriuretic peptide B (NPPB), a peptide with amino acid sequence equivalence to human BNP produced by recombinant DNA technology, is a new generation of anti-HF drug that exhibits significant dilating effects on coronary arteries (Siddique *et al*., 2010; Abou *et al*., 2016; Lesko *et al*., 2017; Pocrnic *et al*., 2020). Metoprolol tartrate is a beta-blocking drug that is mostly used to treat heart failure. Accordingly, 52 patients with AMI-HF treated with metoprolol tartrate combined with NPPB were retrospectively analyzed in this study to explore their clinical efficacy.

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MATERIALS AND METHODS

Inclusion criteria

(1) Patients with acute ST segment elevation AMI was observed; (2) Patients with Killip classification system of II-III; (3) Patients with acute left heart failure; (4) All patients visited within 24 hours after the onset and were in line with WHO's clinical diagnosis of AMI-HF standard; (5) Patients and their families signed the informed consent form after being fully informed of the main purpose and process of the study.

Exclusion criteria

(1) Patients with severe and unstable hypertension; (2) Patients with recent active visceral hemorrhage; (3) Patients with a history of hemorrhagic stroke; (4) Patients with other bleeding diseases; (5) Patients who are allergic to the drugs selected in the study; (6) Patients

with cardiogenic shock; (7) Patients with persistent ventricular tachycardia or persistent atrial fibrillation.

Case screening and grouping

A total of 105 AMI-HF patients were selected in our hospital from January 2020 to June 2021 and divided into Group I (n=53) and Group II (n=52). Both groups received conventional treatment and Group II was additionally treated with metoprolol tartrate tablets and NPPB. The study was carried out with the permission of the hospital ethics committee.

Methods

After admission, all patients underwent all biochemical tests, followed by conventional treatments such as cardiac strengthening, vasodilatation, diuresis, correction of electrolyte disturbances, oxygenation, anti-infection, low-molecular heparin anticoagulation, and anti-arrhythmias (Bocchi *et al*., 2013; Le *et al*., 2017; Zhang *et al*., 2017). Additionally, patients in Group II received metoprolol tartrate tablets in combination with NPPB. Intravenous injection of metoprolol tartrate (specification: 25mg, Heilongjiang Dilong Pharmaceutical Co., Ltd, NMPA Approval Number H20093983) was provided, 2.5-5mg/dose (within 2min), every 5min, 3 times (10-15mg), followed by oral administration of 25-50mg metoprolol 15 minutes later, one dose at every 6-12h for 24-48h, and the dosage was then increased to 50-100mg, twice a day. The first NPPB loading dose of 2μg-kg-1 was administered through an intravenous pulse therapy, followed by an intravenous drip at 8.5ng-kg-1-min-1; the treatment spanned 7d.

Observation indicators

After admission, the patients' general information was recorded, including age, gender, BMI, onset time, systolic blood pressure, creatine kinase MB (CK-MB), serum TnI, BNP, N-terminal pro-brain natriuretic peptide (NT-proBNP), Killip classification, and treatment measures.

An ultrasound instrument (model: Philips 7500) was used to measure the patient's cardiac function indicators through the S3 chest probe, such as left ventricular end diastolic diameter (LVEDd), left ventricular end systolic diameter (LVESD) and left ventricular ejection fraction (LVEF).

Heart rate variability (HRV) detection was conducted through the automatic analysis system by using a Holter Recorder (effective recording time not less than 22h), including standard deviation of the NN intervals (SDNN), standard deviations of 5-min mean values of the NN intervals for each 5-min interval (SDANN), and mean normal to normal (NN) and root mean square of heart beat interval differences (RMSSD) of continuous difference, etc..5 ml of fasting venous blood was collected and centrifuged for 10 min to obtain supernatant, and then stored at low temperature for later use. The levels of BNP or NT-proBNP in patients were determined by immunofluorescence; the levels of serum inflammatory factors including interleukin-6 (IL-6) and hs-CRP were determined by enzyme-linked immunosorbent assay.

During the course of treatment, the occurrence of cardiovascular events such as recurrence of myocardial infarction, sudden cardiac death and arrhythmia was recorded.

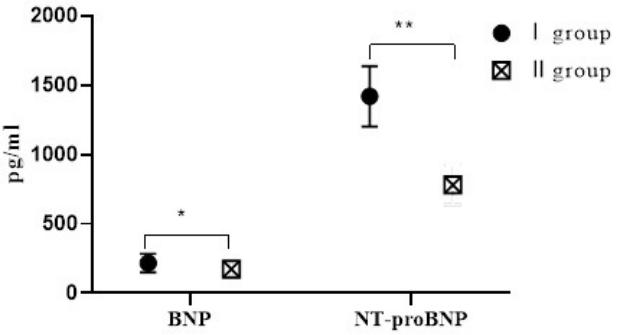
STATISTICAL ANALYSIS

In this study, spss 22.0 software was used for statistical processing, and GraphPad prism 8.0 software for graphic plotting. The count data were compared by X^2 test, which were expressed as [n (%)]. The measurement data were expressed as (x±s), and examined by t test. P<0.05 was considered statistical differences.

RESULTS

General information

The two groups presented no great disparity in terms of general information (p>0.05). See table 1.



Note: The abscissa represents BNP and NT-proBNP, the ordinate represents the detection level, pg/ml;
The BNP and NT-proBNP levels of the patients in Group I after treatment were: (217.25±66.89) and (1420.09±217.36);
The levels of BNP and NT-proBNP after treatment in Group II were: (173.68±60.04) and (781.24±145.28);
*indicates that the BNP levels of the two groups of patients are significantly different (t=3.518, P=0.0006);
**indicates that the NT-proBNP levels of the two groups are significantly different (t=17.612, P<0.001)

Fig. 1: Comparison of the BNP and NT-proBNP levels of the two groups of patients

Comparison of cardiac function indicators

Group II obtained better LVEDD, LVESD, and LVEF than Group I after treatment (p<0.05). See table 2.

Comparison of HRV

The SDNN, SDANN, RMSSD, and PNN50 of both groups witnessed a drastic increase after treatment, with higher results in Group II (p<0.05). See table 3.

Comparison of plasma BNP and NT-proBNP levels

The levels of BNP and NT proBNP in Group II were lower as compared to Group I after treatment (p<0.05), as shown in fig. 1.

Comparison of serum inflammatory factor levels

Group II had remarkably lower IL-6 and hs-CRP levels in relative to the Group I (p<0.05). See table 4.

Comparison of clinical efficacy

Markedly higher clinical response rates were recorded in Group II in comparison with the Group I (P<0.05). See fig. 2.

Comparison of the occurrence of cardiovascular events

Nodistinctive difference was found in incidence the cardiovascular events in two groups (p>0.05), as shown in fig. 3.

Table 1: Comparison of general information

Indicators	Group I (n=53)	Group II (n=52)	X^2/t	P
Age (year)	63.72±12.19	64.13±11.58	0.177	0.860
Gender			0.232	0.630
Male	36 (67.92)	33 (63.46)		
Female	17 (32.08)	19(36.54)		
BMI (kg/m^2)	23.48±2.76	23.65±3.04	0.300	0.765
Onset time (h)	18.45±4.28	17.84±4.31	0.728	0.469
Systolic blood pressure (mmHg)	137.84±23.56	138.42±23.71	0.126	0.900
CK-MB (U/L)	227.58±26.71	227.80±27.06	0.042	0.967
TnI (μg/L)	37.48±3.15	37.59±3.22	0.177	0.860
BNP (pg/ml)	330.12±86.27	331.25±85.81	0.067	0.947
NT-proBNP (pg/ml)	2775.18±326.29	2844.75±365.20	1.030	0.306
Killip classification			0.230	0.632
II	22 (41.51)	24 (46.15)		
III	31 (58.49)	28 (53.85)		
Treatment measures				
Intervention	25 (47.17)	22 (42.31)	0.251	0.616
Drug medication	25 (47.17)	29 (55.77)	0.777	0.378
Thrombolysis	3(5.66)	1 (1.92)	1.001	0.317

Table 2: Comparison of cardiac function between the two groups of patients

Indicators		Group I (n=53)	Group II (n=52)	t/P
LVEDD (mm)	Before treatment	58.52±6.27	58.49±5.81	
	After treatment	56.74±6.20	54.13±4.01	2.556/0.012
LVESD (mm)	Before treatment	45.18±6.29	44.75±6.20	
	After treatment	44.15±6.13	41.26±3.21	3.018/0.003
LVEF (%)	Before treatment	47.25±6.05	47.27±6.23	
	After treatment	51.02±6.17	54.15±6.24	5.584/0.011

Table 3: Comparison of HRV between two groups of patients

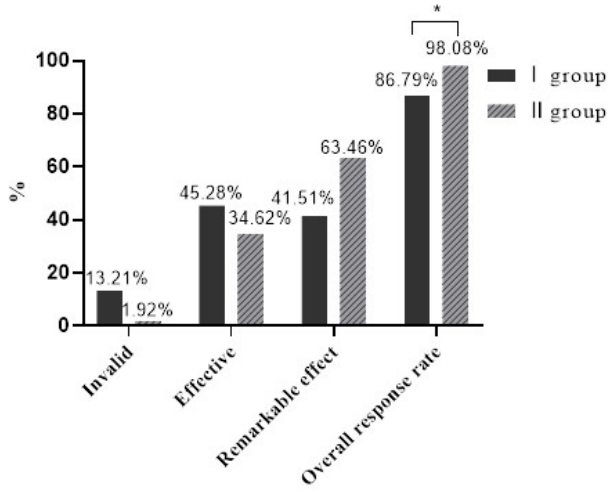
Indicators		Group I (n=53)	Group II (n=52)	t/P
SDNN (ms)	Before treatment	77.03±17.68	77.15±16.88	
	After treatment	79.24±16.15	92.97±18.05	4.109/<0.001
SDANN (ms)	Before treatment	68.95±15.57	70.01±14.83	
	After treatment	72.11±14.86	86.97±17.74	4.656/<0.001
RMSSD	Before treatment	23.18±10.26	23.27±10.31	
	After treatment	24.52±10.42	31.03±10.85	3.136/0.002
PNN50 (%)	Before treatment	8.53±5.66	8.49±6.37	
	After treatment	9.82±5.46	16.07±7.25	4.996/<0.001

Table 4: Comparison of serum inflammatory factor levels between two groups of patients

Indicators		Group I (n=53)	Group II (n=52)	t/P
IL-6 (mg/L)	Before treatment	42.15±3.92	36.13±4.16	
	After treatment	41.94±3.80	26.08±2.23	26.019/<0.001
hs-CRP (ng/L)	Before treatment	36.05±4.21	27.08±3.11	
	After treatment	27.14±3.05	19.58±2.63	13.591/<0.001

DISCUSSION

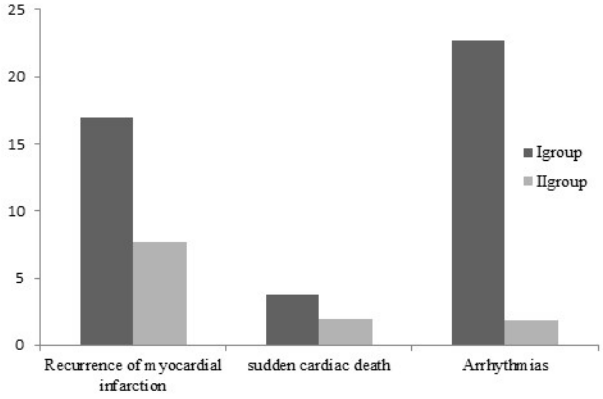
After the onset of AMI, the myocardium innervated by the infarcted vessel would experience ischemia due to a dramatic decrease in blood flow, resulting in abnormal cellular metabolism and supply failure in the body when the new collateral circulation fails to restore blood supply, followed by edema and even necrosis of cardiac myocytes. If the left ventricle is involved, symptoms of heart failure may occur due to cardiac ejection inefficiency (Lanfear *et al*., 2015; Kanumuri *et al*., 2015), which are featured by rapid heart failure, severe chest pain, anxiety and loss of cardiac function. Moreover, the stress response would further induce high levels of neuroendocrine hormone synthesis and secretion to enhance the patient's myocardial contractility and maintain normal function of the body. In contrast, an excessive response would result in excessive peripheral vasoconstriction and a dramatic decrease in glomerular filtration rate, which subsequently leads to water and sodium retention (Rameau *et al*., 2017; Coiro *et al*., 2017; Noori *et al*., 2019). Timely thrombolysis is the mainstay for clinical treatment of AMI-HF with the aim of restoring blood supply to the heart and promoting the recovery of cardiac function by unblocking the infarcted vessels.



Note: The abscissa represents the evaluation dimension, and the ordinate represents the percentage, %;
In Group I, 7 cases were ineffective, 24 cases were effective, 22 cases were markedly effective, and 46 cases were effective in total;
In Group II, 1 case was ineffective, 18 cases were effective, 33 cases were markedly effective, and 51 cases were effective in total;
*indicates a significant difference in the total effective rate of treatment between the two groups of patients (X2=4.749, P=0.029).

Fig. 2: Comparison of clinical efficacy between the two groups of patients (%)

Metoprolol tartrate is a selective β1-adrenergic receptor blocker that attenuates myocardial contraction and reduces myocardial oxygen consumption in patients with HF, thereby effectively avoiding myocardial damage and enhancing cardiomyocyte viability. In patients with acute left ventricular heart failure, metoprolol tartrate blocks the increase in sympathetic activity and reduces the patient's heart rate by decreasing the autoregulation of pacing cells and prolonging supraventricular conduction time (Watanabe *et al*., 2016; Rossello *et al*., 2019; van *et al*., 2020). NPPB is a new anti-HF drug with significant therapeutic effects and its pathological effectiveness is realized by followings. (1) NPPB elevates the serum concentration of cyclic guanosine phosphatase to dilate smooth muscle cells and contribute to vasodilatation, thereby providing a positive balance effect on stressful neuroendocrine hormones after anti-HF. (2) NPPB can act on the renin-angiotensin-aldosterone system to reduce peripheral circulatory resistance and alleviate water and sodium retention by increasing the glomerular filtration rate, which consequently reduces cardiac pre- and afterload and decreases myocardial oxygen consumption (den *et al*., 2010; Husebye *et al*., 2013; Ng 2016; El-Battrawy *et al*., 2018).



Note: The abscissa represents the evaluation dimension and the ordinate represents the percentage, %;
In Group I, 9 cases of myocardial infarction recurrence, 2 cases of sudden cardiac death, and 12 cases of arrhythmia occurred;
In Group II, 4 cases of recurrence of myocardial infarction, 1 case of sudden cardiac death and 5 cases of arrhythmia occurred.

Fig. 3: Comparison of the occurrence of cardiovascular events between the two groups of patients (%)

In this study, Group II obtained better LVEDD, LVESD, and LVEF after treatment (p<0.05), which is consistent with the research results by ITZHAKI (Itzhaki*et al*., 2018). Moreover, the SDNN, SDANN, RMSSD, and PNN50 of both groups all witnessed a drastic increase after treatment, with higher results in Group II (p<0.05); Group II obtained significantly lower levels of B-type natriuretic peptide (BNP) and N-terminal B-type natriuretic peptide precursor (NT proBNP), markedly lower levels in interleukin (IL)-6 and hypersensitive-c-reactive-protein (hs-CRP) in contrast to Group I (p<0.05). Additionally, markedly higher total response rates were observed in Group II (P<0.05); the incidence of

cardiovascular events was not statistically different in two groups (p>0.05). All the above results indicate that the combination treatment of metoprolol tartrate tablets and NPPB yields better outcomes in cardiac function and significantly enhances the early treatment effect of AMI-HF. On top of these, the absence of significant difference in the incidence of cardiovascular events is suggestive of the safety and effectiveness profile.

CONCLUSION

Taken together, the combination of metoprolol tartrate tablets and NPPB is a boon in treating AMI-HF. Nevertheless, the sample size of this study is relatively small, which may result in data bias. In the future, study with larger sample size is required to provide more reliable and robust evidence.

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