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Original Article

Metoprolol combined with amiodarone intervention improves cardiac and immune function in patients with myocardial infarction

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Abstract: Objective: The present study was designed to demonstrate that metoprolol combined with amiodarone could improve the cardiac function and immune function of patients with myocardial infarction (MI). Methods: Totally 148 patients with MI treated in Wuwei People's Hospital of Gansu Province were divided into two groups according to the mode of treatment. Among them, 62 patients in the control group (CG) were treated with metoprolol, and the rest 86 patients in the intervention group (IG) were treated with amiodarone on the basis of the CG. The curative effect and adverse reaction rate of the two groups were recorded. The cardiac function: left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVDD), end-diastolic interventricular septum thickness (IVST) and blood lipids, expression levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) were compared between the two groups before and after treatment. FACSCalibo flow cytometry was employed to detect T lymphocyte subsets in peripheral blood of the two groups. Enzyme-linked immunosorbent assay (ELISA) was applied to measure the concentration of serum inflammatory factors represented by interleukin-6 (IL-6), serum high sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-α (TNF-α) before and after treatment. Logistic regression was adopted to analyze the risk factors affecting the effect of treatment. Results: Compared with the CG, the IG presented markedly better post-treatment cardiac function expression, blood lipid level, and immune function, as well as notably lower levels of inflammatory factors. No adverse reactions occurred in both groups. Multivariate logistic regression analysis demonstrated that gender, history of diabetes, history of hypertension, hyperlipidemia, pretreatment IL-6, hs-CRP, TNF-α levels and treatment methods were independent risk factors that affect the outcome of treatment in patients with MI. Conclusion: The intervention of metoprolol combined with amiodarone could improve the cardiac function of patients with MI, reduce the levels of blood lipids and inflammatory factors, and enhance immune function.

Keywords: Metoprolol combined with amiodarone, myocardial infarction, cardiac function, immune function, risk factors

Introduction

Myocardial infarction (MI) is a complex disease and the leading cause of death worldwide [1, 2], which is caused by the mismatch between substrate supply and oxygen in the myocardium and eventually leads to myocardial ischemia and cell death [3]. According to treatment statistics, nearly 8 million people in the United States suffer from MI every year, and the incidence of men is significantly higher than that of women [4]. Myocardial remodeling after MI often results in increased tissue stiffness and ventricular dysfunction in patients [5]. For the diagnosis of MI, the cardiac troponin level or 12-lead electrocardiogram is usually applied for clinical diagnosis [6]. While its mainstream treatment at present includes non-steroidal anti-inflammatory drugs, oral anticoagulants, clopidogrel, and aspirin, which often lead to cardiovascular death, stroke or non-fatal MI [7]. Although studies have shown that cardiovascular diseases in developed countries tend to decrease due to advances in treatment, the mortality rate of cardiovascular diseases is still high due to the aging and increasing population [8, 9]. Therefore, finding safe and effective treatments has become a clinical priority.

Metoprolol is a β1-adrenoceptor blocker, which can competitively block β 1-adrenoceptor in glomerulus and heart [10]. Studies have shown that it is clinically effective in treating cardiovascular diseases such as arrhythmia, hypertension and MI [11]. In addition, it possesses the property of being easily soluble in water, and can be completely absorbed by patients after oral administration [12]. There is evidence showing that early administration of metoprolol in patients with MI can effectively reduce the infarct area and the severity of infarction [13]. Besides, amiodarone is a lipophilic drug that is reported to be able to prolong the duration of atrial action potential and refractory to reduce early cardiac excitation [14]. It can not only inhibit the passage of K^+, Na^+ and Ca^{2+}, but prevent the excessive production of pro-inflammatory cytokines, exerting a neuroprotective effect against the hemorrhagic brain injury without affecting the heart rhythm and blood pressure of patients [15]. Therefore, amiodarone is given clinically in the treatment of patients with arrhythmias [16]. In a study by Lü et al. [17], the administration of amiodarone plus metoprolol reduced the incidence of cardiac time and readmission rates in patients with chronic heart failure.

Currently, there are few studies on the efficacy and influencing factors of metoprolol combined with amiodarone in the intervention of MI. Therefore in this study, we evaluated the efficacy of the combination of the two therapies and analyzed the influencing factors, hoping to provide clinical reference for the treatment of patients with MI.

Materials and methods

General information

A total of 148 patients with MI admitted to Wuwei People's Hospital of Gansu Province were selected and divided into the IG (86 cases, including 58 males and 28 females, aged 38-78 years) and the CG (62 cases, including 45 males and 17 females, aged 42-79 years). This study was conducted under the approval of Wuwei People's Hospital of Gansu Province Medical Ethics Committee, and the subjects and their guardians were informed and signed the full informed consent. Inclusion criteria: Patients in both groups were diagnosed as MI by electrocardiogram and coronary angiography [18] for the first time, with an estimated survival time of ≥1 month and detailed clinical data. Exclusion criteria: Patients who had taken drugs that might impact the indicators of this study in the past six months, who were allergic to therapeutic drugs, or those who dropped out of the study, complicated with other malignant tumors, or lost to follow-up.

Treatment methods

Patients in both groups were first treated with routine procedures, including antiplatelet, anticoagulant, and oxygen inhalation. Apart from that, the CG was given a single drug treatment: patients were instructed to take metoprolol (Sichuan Ruikang Pharmaceutical Co., Ltd., article number: H20084505) orally at an initial dose of 12.5 mg for 12 h/time. After the cardiac function gradually stabilized, the patient was informed to increase the dose to 25 mg every 24 h, and the dose could be adjusted to 50 mg and 6 h/time according to their cardiac function status. While patients in the IG were orally administrated with amiodarone (Sanofi Aventis (Hangzhou) Pharmaceutical Co., Ltd., item number: H19993254) additionally at 3 d/time, 0.2 mg once, and the dose was adjusted to 2 d/times, 0.2 mg on the seventh day. Patients in both groups were treated continuously for 4 weeks.

Outcome measures

(1) The levels of LVEF, LVDD and IVST before treatment and at 4 weeks after treatment were measured by ultrasonic Doppler blood flow measurement system (Gene & I Scientific Co., Ltd., Beijing, China, Article No.: 0000).

(2) Before treatment and at the fourth week of treatment, patients in both groups were subjected to fasting blood collection of 5 mL and centrifugation at 1500 g and 4°C for 10 min. The serum lipid indexes levels of patients in the two groups, which were TC, TG, LDL-C, and HDL-C, were determined using an automatic chemiluminescence immunoanalyzer (Easydiagnosis Biomedicine Co., Ltd., Wuhan, China, Article No.: CF10), and the test was conducted in strict conformity to the instructions.

(3) The peripheral blood T lymphocyte subsets of the two groups were detected by FACSCalibo flow cytometry (B D line Franklin

Lakes, NJ, USA), and the values of $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ in peripheral blood were read. The experimental procedures were operated in strict accordance with the product instructions.

(4) Inflammatory cytokines: The expression levels of IL-6, hs-CRP and TNF-α in the two groups were detected by ELISA [19] strictly according to the instructions of human IL-6 ELISA, human hs-CRP ELISA and human TNF-α ELISA kits (Qiao Yu Biotechnology Co., Ltd., Shanghai, China, QN-PS0049, QY-Q11400, QN-PS0122).

(5) Efficacy evaluation: Markedly effective: the clinical symptoms disappeared, cardiac function and immune function returned to normal. Effective: the clinical symptoms basically disappeared, and the cardiac function and immune function of the patients were found to be basically normal. Ineffective: there was no improvement in clinical symptoms, nor there was any change in cardiac function and immune function.

Statistical methods

Statistical analysis was performed using SPSS22.0 (Easy Biotechnology Co., Ltd., Beijing, China). The counting data was represented by the number of cases/percentage (n/%), and the inter-group comparison was performed by the Chi-square test. When the theoretical frequency in the chi-square test was less than 5, the continuous correction chi-square test was adopted. The measurement data was expressed as mean ± SM, and the inter-group comparison was conducted using the independent sample t-test, while the intra-group comparison before and after treatment was carried out by the paired t-test. Logistics multivariate regression analysis was responsible for the analysis of risk factors affecting the efficacy of patients with MI. When $P<0.05$, the difference was statistically significant.

Results

General information

There were no significant differences between the two groups in clinical baseline data such as gender, age, history of diabetes, history of hypertension, infarction location, history of smoking, drinking history, and residence ($P>0.05$) (**Table 1**).

Cardiac function indexes before and after treatment

No significant differences were observed in LVEF, LVEDD or IVST between the two groups before treatment ($P>0.05$). While the postoperative LVEF was higher than that of the CG ($P<0.05$), and the LVEDD and IVST after treatment were lower than those of the CG ($P<0.05$) (**Figure 1**).

Blood lipid levels before and after treatment

The levels of TC, TG, LDL-C and HLD-C did not identify any marked differences between the two groups before treatment ($P>0.05$). While compared with the CG, the post-treatment TC, TG and LDL-C levels were lower ($P<0.05$), and the LDL-C level was higher in the IG ($P<0.05$) (**Figure 2**).

Immune function indexes before and after treatment

There were no significant differences in the levels of $CD3^+$, $CD4^+$, $CD8^+$ or $CD4^+/CD8^+$ between the two groups before treatment ($P>0.05$). While after treatment, the levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ in the IG were higher than those in the CG ($P<0.05$), and the level of $CD8^+$ was lower than that in the CG ($P<0.05$) (**Table 2**; **Figure 3**).

Inflammatory factor levels before and after treatment

The levels of IL-6, hs-CRP, and TNF-α before treatment were not statistically different between the two groups of patients ($P>0.05$), but the postoperative IL-6, hs-CRP, and TNF-α levels in the IG were all lower than those in the CG ($P<0.05$) (**Table 3**).

Post-treatment efficacy in the two groups

After treatment, the total effective rate of the IG was 91.86%, while that of the CG was 77.42%. It was obvious that the total effective rate of the IG was higher than that of the CG ($P<0.05$). In addition, there were no adverse reactions in both groups after treatment (**Table 4**).

Table 1. Comparison of general information between the two groups [n (%)] (x ± sd)

Categories	IG (n = 86)	CG (n = 62)	t/χ^2 value	*P* value
Gender			0.450	0.503
Male	58 (67.44)	45 (72.58)		
Female	28 (32.56)	17 (27.42)		
Age (years old)			0.851	0.356
<55	31 (36.05)	27 (43.55)		
≥55	55 (63.95)	35 (56.45)		
History of diabetes			0.531	0.466
Yes	63 (73.26)	42 (67.74)		
No	23 (26.74)	20 (32.26)		
History of hypertension			0.919	0.338
Yes	59 (68.60)	47 (75.81)		
No	27 (31.40)	15 (24.19)		
Infarction location			0.681	0.878
Extensive anterior wall	14 (16.28)	11 (17.74)		
Anterior septal wall	23 (26.74)	19 (30.65)		
Anterior septal wall combined with right ventricle	31 (36.05)	22 (35.48)		
Inferior wall	18 (20.93)	10 (16.13)		
Smoking history			1.969	0.161
Yes	47 (54.65)	41 (66.13)		
No	39 (45.35)	21 (33.87)		
Drinking history			0.196	0.658
Yes	51 (59.30)	39 (62.90)		
No	35 (40.70)	23 (37.10)		
Residence			0.280	0.598
Rural	55 (63.95)	37 (59.68)		
Urban	31 (36.05)	25 (40.32)		

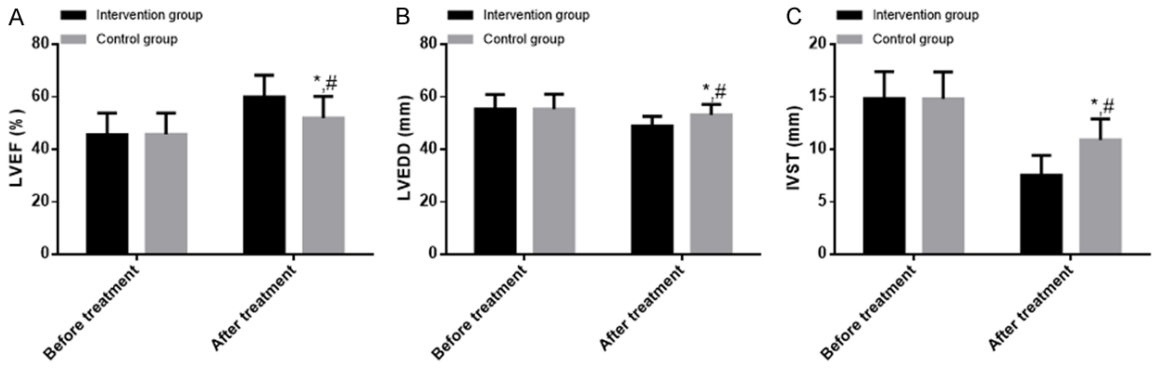

Figure 1. Cardiac function indexes before and after treatment. A. The postoperative LVEF in the IG was higher than that in the CG. B. The postoperative LVEDD in the IG was lower than that in the CG. C. The postoperative IVST in the IG was lower than that in the CG. Note: *indicated P<0.05 compared with before treatment, and #indicated P<0.05 compared with CG after treatment.

Risk factors that affected the outcome of patients with MI

In this section, we compared the differences in clinical parameters and related indicators of patients with effective and ineffective treatment. The results showed that there were 127 effective patients and 21 ineffective patients, and there was no significant difference in age, infarction location or residence

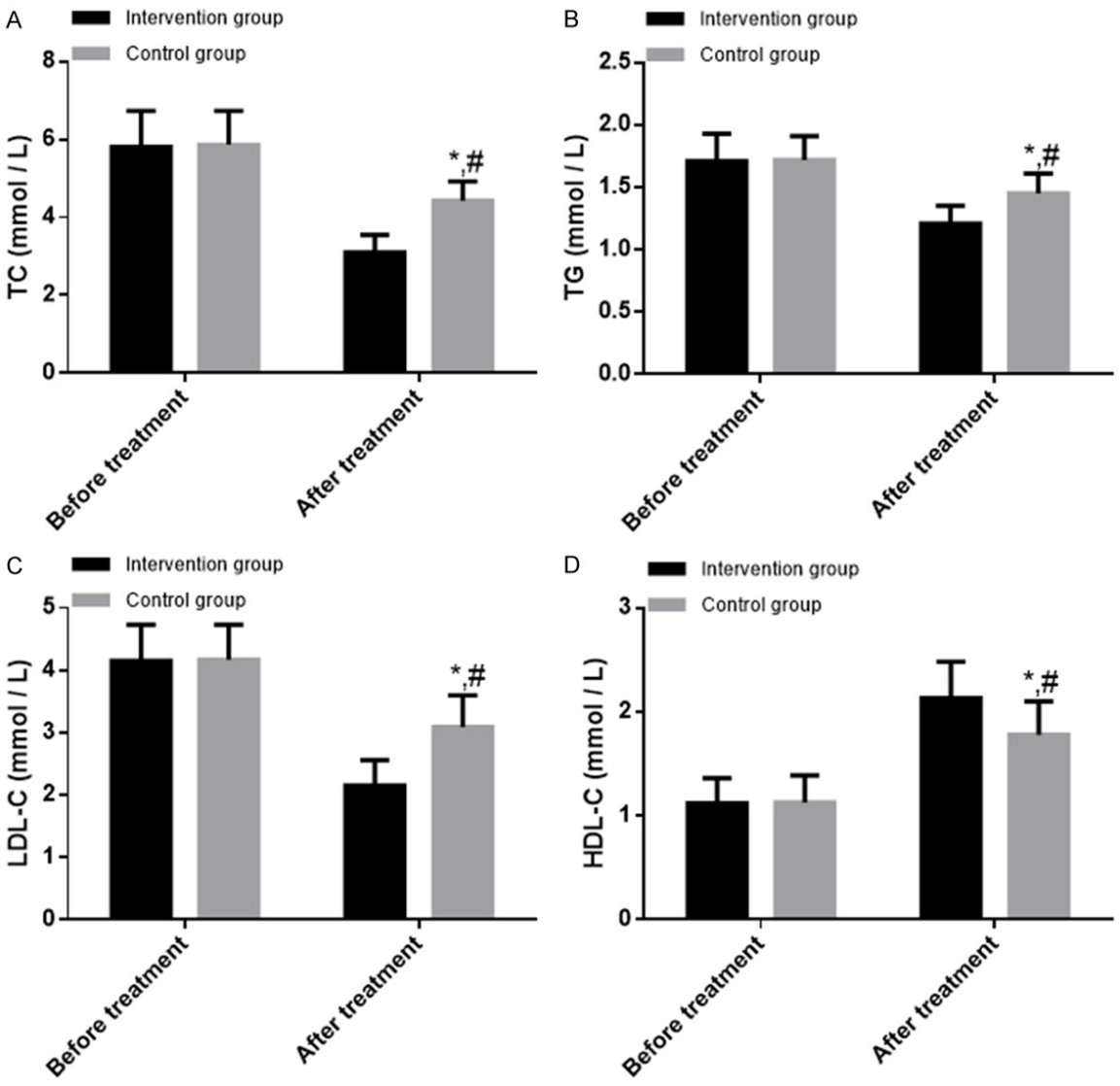

Figure 2. Blood lipid levels before and after treatment. A. The postoperative TC level in the IG was lower than that in the CG. B. The postoperative TG level in the IG was lower than that in the CG. C. The postoperative LDL-C level in the IG was lower than that in the CG. D. The postoperative HLD-C level in the IG was higher than that in the CG. Note: *indicated P<0.05 compared with that before treatment, and #indicated P<0.05 compared with CG after treatment.

Table 2. Comparison of immune function indexes before and after treatment (x ± sd)

Groups	$CD3^+$ (%)		$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
IG (n = 86)	55.45±6.24	68.14±7.32	34.13±4.34	42.45±5.21	30.14±3.45	23.12±3.24	1.13±0.33	1.68±0.42
CG (n = 62)	55.69±6.21	60.45±7.21	34.56±4.42	38.43±5.12	29.85±3.32	26.31±3.34	1.15±0.34	1.45±0.41
t	0.231	6.345	0.590	4.665	0.513	5.834	0.359	3.320
P	0.817	<0.001	0.556	<0.001	0.609	<0.001	0.720	0.001

between effective and ineffective patients (P>0.05). However, there were significant differences in gender, history of diabetes, history of hypertension, smoking history, drinking history, hyperlipidemia, IL-6, hs-CRP, TNF-α and treatment methods (P<0.05). Finally, we performed

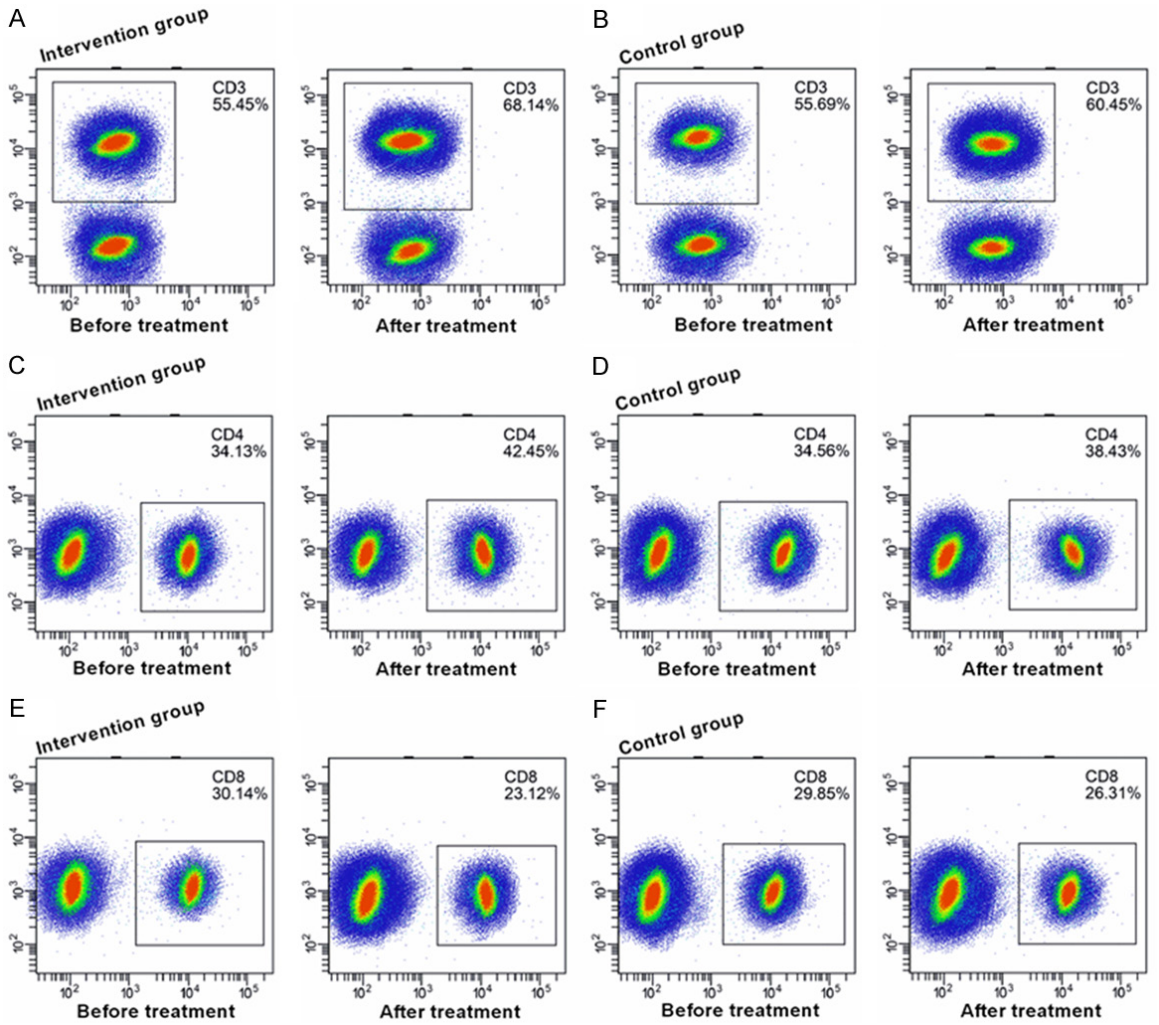

Figure 3. Immune function indexes before and after treatment. A, B. Flow cytometry of $CD3^+$ in the IG and the CG before and after treatment. C, D. Flow cytometry of $CD4^+$ in the IG and the CG before and after treatment. E, F. Flow cytometry of $CD8^+$ in the IG and the CG before and after treatment.

Table 3. Inflammatory factor levels before and after treatment (x±sd)

Groups	n	IL-6 (ng/L)		hs-CRP (mg/L)		TNF-α (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
IG	86	23.52±2.65	9.12±1.21	8.08±1.21	5.23±0.63	13.47±2.02	7.96±0.87
CG	62	23.14±2.34	16.31±2.04	8.13±1.24	7.53±0.81	13.75±1.85	10.93±1.46
t	-	0.903	26.810	0.246	19.420	0.862	15.450
P	-	0.368	<0.001	0.806	<0.001	0.390	<0.001

Table 4. Post-treatment efficacy in the two groups

Groups	n	Markedly effective	Effective	Ineffective	Total effective rate (%)
IG	86	61 (70.93)	18 (20.93)	7 (8.14)	79 (91.86)
CG	62	23 (37.10)	25 (40.32)	14 (22.58)	48 (77.42)
χ^2 value	-	-	-	-	6.171
P value	-	-	-	-	0.013

multivariate logistic regression analysis on the different factors. The results revealed that gender (P = 0.023), history of diabetes (P = 0.025), history of hypertension (P = 0.028), hyperlipidemia (P = 0.022), IL-6 (P = 0.019), hs-CRP (P = 0.011), TNF-α (P = 0.017), and treatment

Table 5. Univariate analysis of poor prognosis in patients with MI [n (%), x ± sd]

Factors	n	Effective group (n = 127)	Ineffective group (n = 21)	χ^2/t	P
Gender				5.043	0.025
Male	103	84 (81.55)	19 (18.45)		
Female	45	43 (95.56)	2 (4.44)		
Age (years old)				1.787	0.181
<55	58	47 (81.03)	11 (8.97)		
≥55	90	80 (88.89)	10 (11.11)		
History of diabetes				4.529	0.033
Yes	105	86 (81.90)	19 (18.10)		
No	43	41 (95.35)	2 (4.65)		
History of hypertension				6.715	0.010
Yes	106	86 (81.13)	20 (18.87)		
No	42	41 (97.62)	1 (2.38)		
Infarction location				0.735	0.865
Extensive anterior wall	25	21 (84.00)	4 (16.00)		
Anterior septal wall	42	36 (85.71)	6 (14.29)		
Anterior septal wall combined with right ventricle	53	47 (88.68)	6 (11.32)		
Inferior wall	28	23 (82.14)	5 (17.86)		
Smoking history				6.998	0.008
Yes	88	70 (79.55)	18 (20.45)		
No	60	57 (95.00)	3 (5.00)		
Drinking history				4.166	0.041
Yes	90	73 (81.11)	17 (18.89)		
No	58	54 (93.10)	4 (6.90)		
Residence				0.262	0.609
Rural	92	80 (13.04)	12 (13.04)		
Urban	56	47 (83.93)	9 (16.07)		
Hyperlipidemia				3.916	0.048
Yes	91	74 (81.32)	17 (18.68)		
No	57	54 (92.98)	4 (7.02)		
Immune function				1.48	0.223
Normal	120	105 (87.50)	15 (12.50)		
Reduced	28	22 (78.57)	6 (21.43)		
IL-6 (ng/L)	148	9.02±1.21	18.52±2.35	28.370	<0.001
hs-CRP (mg/L)	148	5.43±0.63	8.28±1.23	16.320	<0.001
TNF-α (ng/L)	148	7.46±0.87	11.47±2.12	15.110	<0.001
Treatment methods				5.246	0.022
Conventional treatment	86	69 (80.23)	17 (19.77)		
Metoprolol treatment	62	58 (93.55)	4 (6.45)		

methods (P = 0.008) were independent risk factors that affected the treatment effect of patients with MI (**Tables 5-7**).

Discussion

Myocardial infarction (MI) is a common clinical disease with intricate pathogenesis [20]. Clinical studies have revealed that the incidence of MI has been on the rise [21]. Although the progress in the diagnosis and treatment of MI has greatly improved the survival rate of patients [22], it is still prone to poor prognosis [23]. Therefore, we focused on the study of the treatment of MI and the factors influencing the efficacy, aiming to provide effective clinical treatment options for patients.

Table 6. Logistic multivariate regression analysis assignment

Factors	Variables	Assignments
Gender	X1	Male = 0, female = 1
History of diabetes mellitus	X2	No = 0, yes = 1
History of hypertension	X3	No = 0, yes = 1
Smoking history	X4	No = 0, yes = 1
Drinking history	X5	No = 0, yes = 1
Hyperlipidemia	X6	No = 0, yes = 1
IL-6 (ng/L)	X7	Raw data analysis for continuous variables.
hs-CRP (mg/L)	X8	Raw data analysis for continuous variables.
TNF-α (ng/L)	X9	Raw data analysis for continuous variables.
Treatment methods	X10	Conventional treatment = 0, metoprolol treatment = 1

Table 7. Multivariate Logistic regression analysis of factors affecting the efficacy of patients with MI

Variables	B	S.E	Wals	P	OR	95% CI
Gender	1.134	0.472	5.338	0.023	2.341	1.251-6.022
History of diabetes	1.997	0.694	5.312	0.025	1.132	0.542-2.363
History of hypertension	2.116	0.749	6.981	0.028	1.592	1.024-2.438
Smoking history	0.123	0.032	3.674	0.961	0.482	0.155-1.274
Drinking history	0.338	0.108	9.935	0.650	1.133	0.362-4.251
Hyperlipidemia	0.621	0.252	6.835	0.022	1.851	1.462-2.563
IL-6 (ng/L)	1.338	0.708	9.935	0.019	3.212	1.605-6.420
hs-CRP (mg/L)	1.161	0.507	4.768	0.011	3.181	1.591-6.362
TNF-α (ng/L)	1.239	0.557	5.023	0.017	3.194	1.597-6.388
Treatment methods	2.345	0.978	5.308	0.008	5.413	2.707-10.826

Many clinical studies have reported the treatment methods and efficacy of MI. For example, in the study of Koch-Weser et al. [24], long-term use of metoprolol in patients with MI can reduce mortality and the occurrence of infarction. In addition, according to Sattler et al. [25], amiodarone intervention in acute MI can prevent the occurrence of ventricular fibrillation and has an impact on blood pressure and cardiac output. In this study, the cardiac function indexes levels of the IG after treatment were better than those of the CG, indicating that metoprolol combined with amiodarone could better inhibit the myocardial contraction of the patients and reduce myocardial oxygen consumption. There is also research demonstrating that abnormalities in lipid metabolism and function are related to the pathological mechanism of myocardial I/R injury, and that abnormal lipid metabolism produced marked effects on patients with myocardial injury [26]. In current study, the blood lipid levels of the IG were superior to that of the CG, suggesting that metoprolol combined with amiodarone could reduce the levels of lipoprotein and cholesterol in patients. Some studies have shown that the T cell immune function of patients with acute MI will decrease, and that the attack of acute MI is associated with different degrees of immune dysfunction [27]. The results of this study exhibited that the indexes of immune function in the IG after treatment were better than those in the CG, indicating that metoprolol combined with amiodarone could adjust the basic immune function, normalize the abnormal and disordered functions, and thus enhance the immune function.

Irrespective of acute inflammatory response MI brings, it also causes psychological failure in patients. Studies have shown that the increase of CRP, TNF-α and MCP-1 in inflammatory factors will lead to the risk of MI [28]. Therefore, we measured the serum factor levels of patients, and the results showed that the levels of IL-6, hs-CRP, and TNF-α in the IG were significantly lower than those in the CG after treatment, suggesting that metoprolol combined with amiodarone was more conducive to improving the inflammatory response of patients. Moreover, the total effective rate (91.86%) of the IG was significantly higher than that of the CG (77.42%), plus that there was no adverse reaction in both groups, indicating that

metoprolol combined with amiodarone was more effective. Finally, we performed a risk factor analysis. The results demonstrated that pretreatment levels of IL-6, hs-CRP, TNF-α, gender, history of diabetes, history of hypertension, hyperlipidemia, and treatment methods were independent risk factors influencing the treatment effect of MI patients, which was basically in line with the study conducted by Ognev et al. [29], that hypertension, smoking history, and hypercholesterolemia were the main risk factors affecting MI.

In conclusion, metoprolol combined with amiodarone intervention can improve cardiac function in patients with MI, reduce the level of blood lipid and inflammatory factors, and enhance immune function. However, there is still room for improvement in this study. For example, we can supplement the basic experiments of the treatment mechanism of the two treatment methods to explore the risk factors that affect the efficacy of patients from the molecular level. Furthermore, we can add the analysis of cognitive function and quality of life of the patients not observed in the study. In the future, we will gradually improve our research from the above perspectives.

Disclosure of conflict of interest

None.

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References

[1] Do R, Stitziel NO, Won HH, Jorgensen AB, Duga S, Angelica Merlini P, Kiezun A, Farrall M, Goel A, Zuk O, Guella I, Asselta R, Lange LA, Peloso GM, Auer PL, Project NES, Girelli D, Martinelli N, Farlow DN, DePristo MA, Roberts R, Stewart AF, Saleheen D, Danesh J, Epstein SE, Sivapalaratnam S, Hovingh GK, Kastelein JJ, Samani NJ, Schunkert H, Erdmann J, Shah SH, Kraus WE, Davies R, Nikpay M, Johansen CT, Wang J, Hegele RA, Hechter E, Marz W, Kleber ME, Huang J, Johnson AD, Li M, Burke GL, Gross M, Liu Y, Assimes TL, Heiss G, Lange EM, Folsom AR, Taylor HA, Olivieri O, Hamsten A, Clarke R, Reilly DF, Yin W, Rivas MA, Donnelly P, Rossouw JE, Psaty BM, Herrington DM, Wilson JG, Rich SS, Bamshad MJ, Tracy RP, Cupples LA, Rader DJ, Reilly MP, Spertus JA, Cresci S, Hartiala J, Tang WH, Hazen SL, Allayee H, Reiner AP, Carlson CS, Kooperberg C, Jackson RD, Boerwinkle E, Lander ES, Schwartz SM, Siscovick DS, McPherson R, Tybjaerg-Hansen A, Abecasis GR, Watkins H, Nickerson DA, Ardissino D, Sunyaev SR, O'Donnell CJ, Altshuler D, Gabriel S and Kathiresan S. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. Nature 2015; 518: 102-106.

[2] Horckmans M, Ring L, Duchene J, Santovito D, Schloss MJ, Drechsler M, Weber C, Soehnlein O and Steffens S. Neutrophils orchestrate post-myocardial infarction healing by polarizing macrophages towards a reparative phenotype. Eur Heart J 2017; 38: 187-197.

[3] Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, Arefalk G, Frick M, Alfredsson J, Nilsson L, Ravn-Fischer A, Omerovic E, Kellerth T, Sparv D, Ekelund U, Linder R, Ekstrom M, Lauermann J, Haaga U, Pernow J, Ostlund O, Herlitz J and Svensson L; DETO2X–SWEDEHEART Investigators. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med 2017; 377: 1240-1249.

[4] Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E and Sabatine MS; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015; 372: 1791-1800.

[5] Garza MA, Wason EA and Zhang JQ. Cardiac remodeling and physical training post myocardial infarction. World J Cardiol 2015; 7: 52-64.

[6] Reichlin T, Twerenbold R, Wildi K, Gimenez MR, Bergsma N, Haaf P, Druey S, Puelacher C, Moehring B, Freese M, Stelzig C, Krivoshei L, Hillinger P, Jager C, Herrmann T, Kreutzinger P, Radosavac M, Weidmann ZM, Pershyna K, Honegger U, Wagener M, Vuillomenet T, Campodarve I, Bingisser R, Miro O, Rentsch K, Bassetti S, Osswald S and Mueller C. Prospective validation of a 1-hour algorithm to rule-out and rule-in acute myocardial infarction using a high-sensitivity cardiac troponin T assay. CMAJ 2015; 187: E243-E252.

[7] Schjerning Olsen AM, Gislason GH, McGettigan P, Fosbol E, Sorensen R, Hansen ML, Kober L, Torp-Pedersen C and Lamberts M. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA 2015; 313: 805-814.

[8] Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M and Janzon M. Cardiovascular risk in post-myocardial infarction patients: na-

tionwide real world data demonstrate the importance of a long-term perspective. Eur Heart J 2015; 36: 1163-1170.
[9] Ouweneel DM, Eriksen E, Sjauw KD, van Dongen IM, Hirsch A, Packer EJ, Vis MM, Wykrzykowska JJ, Koch KT, Baan J, de Winter RJ, Piek JJ, Lagrand WK, de Mol BA, Tijssen JG and Henriques JP. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol 2017; 69: 278-287.
[10] Rossi P, Paoli P, Chelazzi L, Conti L and Bencini A. The solid-state structure of the beta-blocker metoprolol: a combined experimental and in silico investigation. Acta Crystallogr C Struct Chem 2019; 75: 87-96.
[11] Emami J and Kazemali MR. Design and in vitro evaluation of a novel controlled onset extended-release delivery system of metoprolol tartrate. Res Pharm Sci 2016; 11: 81-92.
[12] Allam A and Fetih G. Sublingual fast dissolving niosomal films for enhanced bioavailability and prolonged effect of metoprolol tartrate. Drug Des Devel Ther 2016; 10: 2421-2433.
[13] Garcia-Prieto J, Villena-Gutierrez R, Gomez M, Bernardo E, Pun-Garcia A, Garcia-Lunar I, Crainiciuc G, Fernandez-Jimenez R, Sreeramkumar V, Bourio-Martinez R, Garcia-Ruiz JM, Del Valle AS, Sanz-Rosa D, Pizarro G, Fernandez-Ortiz A, Hidalgo A, Fuster V and Ibanez B. Neutrophil stunning by metoprolol reduces infarct size. Nat Commun 2017; 8: 14780.
[14] Garcia JR, Campbell PF, Kumar G, Langberg JJ, Cesar L, Deppen JN, Shin EY, Bhatia NK, Wang L, Xu K, Schneider F, Robinson B, Garcia AJ and Levit RD. Minimally invasive delivery of hydrogel-encapsulated amiodarone to the epicardium reduces atrial fibrillation. Circ Arrhythm Electrophysiol 2018; 11: e006408.
[15] Kotoda M, Ishiyama T, Mitsui K, Hishiyama S and Matsukawa T. Neuroprotective effects of amiodarone in a mouse model of ischemic stroke. BMC Anesthesiol 2017; 17: 168.
[16] Hashmi A, Keswani NR, Kim S and Graham DY. Hepatic dysfunction in patients receiving intravenous amiodarone. South Med J 2016; 109: 83-86.
[17] Lu HS, He BB and Huang GH. [Therapeutic effects of amiodarone and metoprolol on chronic heart failure complicated by ventricular arrhythmia]. Nan Fang Yi Ke Da Xue Xue Bao 2009; 29: 1240-1242.
[18] Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, Atar D, Kaski JC, Sechtem U and Tornvall P; WG on Cardiovascular Pharmacotherapy. ESC working group position paper on myocardial infarction with nonobstructive coronary arteries. Eur Heart J 2017; 38: 143-153.
[19] Yavas O, Acimovic SS, Garcia-Guirado J, Berthelot J, Dobosz P, Sanz V and Quidant R. Self-calibrating on-chip localized surface plasmon resonance sensing for quantitative and multiplexed detection of cancer markers in human serum. ACS Sens 2018; 3: 1376-1384.
[20] Oikawa FTC, Hueb W, Nomura CH, Hueb AC, Villa AV, da Costa LMA, de Melo RMV, Rezende PC, Segre CAW, Garzillo CL, Lima EG, Ramires JAF and Filho RK. Abnormal elevation of myocardial necrosis biomarkers after coronary artery bypass grafting without established myocardial infarction assessed by cardiac magnetic resonance. J Cardiothorac Surg 2017; 12: 122.
[21] Chen WW, Gao RL, Liu LS, Zhu ML, Wang W, Wang YJ, Wu ZS, Li HJ, Gu DF, Yang YJ, Zheng Z, Jiang LX and Hu SS. China cardiovascular diseases report 2015: a summary. J Geriatr Cardiol 2017; 14: 1-10.
[22] McManus DD, Chinali M, Saczynski JS, Gore JM, Yarzebski J, Spencer FA, Lessard D and Goldberg RJ. 30-year trends in heart failure in patients hospitalized with acute myocardial infarction. Am J Cardiol 2011; 107: 353-359.
[23] Hung J, Teng TH, Finn J, Knuiman M, Briffa T, Stewart S, Sanfilippo FM, Ridout S and Hobbs M. Trends from 1996 to 2007 in incidence and mortality outcomes of heart failure after acute myocardial infarction: a population-based study of 20,812 patients with first acute myocardial infarction in Western Australia. J Am Heart Assoc 2013; 2: e000172.
[24] Koch-Weser J. Drug therapy: metoprolol. N Engl J Med 1979; 301: 698-703.
[25] Sattler SM, Lubberding AF, Skibsbye L, Jabbari R, Wakili R, Jespersen T and Tfelt-Hansen J. Amiodarone treatment in the early phase of acute myocardial infarction protects against ventricular fibrillation in a porcine model. J Cardiovasc Transl Res 2019; 12: 321-330.
[26] Feng L, Yang J, Liu W, Wang Q, Wang H, Shi L, Fu L, Xu Q, Wang B and Li T. Lipid biomarkers in acute myocardial infarction before and after percutaneous coronary intervention by lipidomics analysis. Med Sci Monit 2018; 24: 4175-4182.
[27] Yan W, Song Y, Zhou L, Jiang J, Yang F, Duan Q, Che L, Shen Y, Song H and Wang L. Immune cell repertoire and their mediators in patients with acute myocardial infarction or stable angina pectoris. Int J Med Sci 2017; 14: 181-190.
[28] Fang L, Moore XL, Dart AM and Wang LM. Systemic inflammatory response following acute myocardial infarction. J Geriatr Cardiol 2015; 12: 305-312.
[29] Ognev VA, Podpriadova AA and Lisova AV. Identification and assessment of risk factors role in myocardial infarction development. Wiad Lek 2019; 72: 779-783.