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Original Research Article

Efficacy and safety of combination of ulinastatin and meglumine cyclic adenosine monophosphate in the treatment of acute myocardial infarction, and its effect on serum levels of hs-CRP, cTnI and CK

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Abstract

Purpose: *To determine the efficacy and safety of a combination of ulinastatin and meglumine cyclic adenosine monophosphate (cAMP) in the treatment of acute myocardial infarction (AMI), and its effect on serum levels of hypersensitive-c-reactive protein (hs-CRP), cardiac troponin I (cTnI), creatine kinase (CK).*
Methods: *A total of 90 AMI patients admitted to The Second Affiliated Hospital of Qiqihar Medical College, Qiqihar City, Heilongjiang Province, China from January 2019 to January 2020 were selected and randomized (in a 1:1 ration) into control group and study group. Patients in the two groups received meglumine cAMP, while those in the study group were, in addition, treated with ulinastatin. The two groups were compared with regard to clinical efficacy, cardiac function indices, serum biochemical indices, incidence of drug-related side effects, duration and number of episodes of angina pectoris, and levels of neuroendocrine hormones.*
Results: *The study group exhibited remarkably higher treatment effectiveness and cardiac function indices compared to the control group ($p < 0.05$). However, lower levels of serum biochemical indices, lower total incidence of drug toxicity, smaller number and shorter duration of angina pectoris, and lower levels of panel reactive antibodies (PRA) were observed in the study when compared to control group ($p < 0.001$).*
Conclusion: *Treatment of AMI patients with the combination of ulinastatin and meglumine cAMP significantly reduces the clinical symptoms of the patients, with remarkable efficacy and high safety. Furthermore, it down-regulates serum levels of hs-CRP, cTnI and CK. Thus, the combination treatment seems superior to the conventional therapy.*

Keywords: *Ulinastatin, Meglumine cyclic adenosine monophosphate, Acute myocardial infarction*

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INTRODUCTION

Acute myocardial infarction (AMI) is a far commoner diseases in cardiovascular medicine to which the middle-aged and elderly population are most susceptible. However, the incidence of AMI has been showing an upward trend among young people [1,2]. The pathogenesis of AMI is

associated with atherosclerosis, which is basically related to smoking, hypertension, obesity, diabetes and genetic factors [3-5].
AMI is manifested by chest pain, arrhythmia, shock and heart failure. A cascade of complications may be triggered by delayed treatment of AMI, such as heart rupture, post-myocardial infarction syndrome, and embolism. This takes a toll on patient's health and quality of life. Moreover, if prompt and effective nursing measures are not provided, the patient may suffer negative emotions such as depression and anxiety, which make the treatment ineffective and prolong the recovery of physical function [6,7]. Meglumine cyclic adenosine monophosphate (cAMP), a non-digital cardiotonic agent, substantially ameliorates myocardial pumping function and reduces myocardial oxygen consumption. However, it has been clinically found that monotherapy with meglumine cAMP in AMI patients has some limitations in that it does not result in promising therapeutic effect and high safety [8-10]. However, combined treatment of AMI patients with ulinastatin and meglumine cAMP results in significant clinical effects.

The present study was conducted to determine the efficacy and safety of ulinastatin + meglumine cAMP in the treatment of AMI patients. Moreover, the effect of the combined treatment on serum levels of hs-CRP, cTnI and CK was investigated.

METHODS

General information on patients

Between January 2019 and January 2020, ninety AMI patients who were admitted to our hospital were selected and assigned to control and study groups at a ratio of 1:1.

Eligibility and screening

Patients who met the diagnostic criteria of AMI, and patients with first onset of AMI, without a history of similar condition in the past, were included in the study, whereas *p*atients with onset time > 24 h; patients who were allergic to the drugs used in the study, and patients with severe infection, malignant tumor, and immune dysfunction, were assessed as ineligible participants.

The protocol was reviewed and approved by the Ethical Committee of The Second Affiliated Hospital of Qiqihar Medical College Hospital, and also followed international guidelines for human studies. The patients voluntarily signed informed consent form.

Treatments

The two groups of patients were given basic treatments, including anticoagulant, diuresis, oxygen inhalation, and anti-thrombotic therapies. Thereafter, patients in both groups were treated with meglumine cAMP (Changchun Dazheng Pharmaceutical Technology Co. Ltd.; NMPA approval number: H20057048; specification: 60 mg in 5 mL). Glucose injection (5 %; 200 – 500 mL) was used to dilute the meglumine cAMP prior to injection via the intravenous route (60 – 180 mg at a time), once daily.

In addition, the experimental group received ulinastatin (Guangdong Tianpu Biochemical Pharmaceutical Co. Ltd.; NMPA approval number: H20040506; specification: 100,000 units/2 mL). At the initial stage, 100,000 units of ulinastatin was dissolved in 500 mL of 5 % glucose or 0.9 % sodium chloride prior to administration via intravenous drip for 1 - 2 h, 1 - 3 times daily. The dose was adjusted as appropriate, based on the actual condition of the patient.

Evaluation of indices

Clinical efficacy was determined and compared. Efficacy was categorized as *significantly effective* {patient's clinical symptoms disappeared, normalization of electrocardiogram (ECG), absence of angina pectoris, or 80 % reduction in the number of angina pectoris, relative to pre-treatment value}; *effective* (improvement in patient's clinical symptoms and ECG, 50 - 80 % reduction in number of angina pectoris, relative to pre-treatment levels), or *ineffective* (patient's clinical symptoms, number of angina pectoris, and ECG remained unchanged or even got worse, relative to pre-treatment values).

An echocardiograph (Zhuhai Hongbang Medical Technology Co. Ltd, model: HB1012) was employed to assess cardiac function indexes in the two groups. The cardiac function indexes were heart stroke volume (SV), cardiac output (CO), and left ventricular ejection fraction (LVEF).

Morning fasting cubital venous blood (3 mL) was collected from all patients, and centrifuged to obtain sera samples. Then, enzyme-linked immunosorbent assay (ELISA) was used to determine serum levels of hs-CRP, cTnI and CK before and after treatment in the two groups. The assay was carried out following the kit

instructions and procedures. All kits were purchased from Merck Biologicals.

Statistical analysis

Data processing was done with SPSS 20.0, while GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used to visualize graphics. Count data was statistically analyzed with χ^2 test, while measurement data were processed via *t*-test and normality test. Values of $p < 0.05$ were considered statistically significant.

RESULTS

General patient information

The baseline data for the two groups were well-balanced with respect to age, gender, BMI, course of the disease, HAD score, smoking, drinking, and place of ($p > 0.05$, Table 1).

Clinical efficacy

The study group had a significantly higher total treatment effectiveness than the control group ($p < 0.05$; Table 2).

Cardiac function indices

Levels of cardiac function indexes were higher in the study group versus control group ($p < 0.05$; Table 3).

Serum biochemical indices

Table 4 shows that post-treatment levels of serum biochemical indices were significantly lower in the study group versus control group ($p < 0.05$).

Table 1: General information on patients

	Study group (n=45)	Control group (n=45)	χ^2 or *t*	*P*-value
Age (years)	56.75±3.32	56.69±3.29	0.129	0.898
Gender			0.178	0.673
Male	23（51.11）	21（46.67）		
Female	22（48.89）	24（53.33）		
BMI（kg/m^2）	26.27±1.59	25.89±1.63	1.119	0.266
Course of disease (days)	4.12±1.21	4.13±1.11	0.041	0.968
HAD scores	35.52±2.16	35.71±2.08	0.425	0.672
Smoking habit			0.045	0.832
Yes	20（44.44）	21（46.67）		
No	25（55.56）	24（53.33）		
Drinking habit			0.178	0.673
Yes	22（48.89）	24（53.33）		
No	23（51.11）	21（46.67）		
Place of residence			0.050	0.822
Urban	31 (68.89)	30 (66.67)		
Rural	14 (31.11)	15 (33.33)		

Table 2: Comparison of clinical efficacy between the two groups [n (%)], N = 45

Group	Significantly effective	Effective	Ineffective	Total effectiveness
Study	66.67% (30/45)	31.11% (14/45)	2.22% (1/45)	97.78% (44/45)
Control	46.67% (21/45)	26.67% (12/45)	26.67% (12/45)	73.33% (33/45)
χ^2				10.879
P				< 0.05

Table 3: Comparison of cardiac function indexes between the two groups (mean ± SD, n = 45))

Group	SV (mL)		CO (L/min)		LVEF (%)	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*
Study	43.39±4.98	59.63±5.37	3.11±0.49	5.41±0.49	35.22±2.37	51.25±5.39
Control	44.11±4.85	51.23±4.31	3.15±0.34	4.43±0.41	34.93±2.41	41.88±4.12
t	0.695	8.183	0.449	10.289	0.576	13.224
P-value	0.489	< 0.001	0.654	< 0.001	0.566	< 0.001

Table 4: Comparison of serum biochemical indices between the two groups ($\bar{x} \pm s$)

Group	hs-CRP (mg/L)		cTnI (μg/L)		CK (U/dL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study	16.55±2.37	4.85±1.02	14.89±3.37	4.13±1.12	250.33±25.58	129.35±11.48
Control	16.48±2.51	11.03±1.16	15.11±3.29	8.64±1.23	249.98±26.37	187.67±12.01
t	0.136	26.839	0.313	18.187	0.064	23.548
P-value	0.892	< 0.001	0.755	< 0.001	0.949	< 0.001

Table 5: Comparison of incidence of drug toxicity between the two groups [n (%)], N = 45

Group	Nausea	Vomiting	Palpitations	Flustered	Incidence of drug reactions
Study	0.00（0/45）	0.00（0/45）	0.00（0/45）	2.22（1/45）	2.22（1/45）
Control	4.44（2/45）	2.22（1/45）	4.44（2/45）	4.44（2/45）	15.56（7/45）
χ^2					4.939
P-value					< 0.05

Incidence of adverse drug reactions

Patients who received combined treatment had lower total incidence of adverse drug reactions than those in the control group ($p < 0.05$; Table 5).

Number and duration of angina pectoris

Compared to the control group, patients in the study group had more favorable outcomes in terms of the number and duration of angina pectoris after treatment ($p < 0.05$). The numbers of angina pectoris episodes before and after treatment in the study group were 5.39 ± 0.39 and 1.05 ± 0.12 times·week^{-1}, respectively; the numbers of angina pectoris attacks before and after treatment in the control group were 5.41 ± 0.35 and 3.61 ± 0.24 times·week^{-1}, respectively. The durations of angina pectoris before and after treatment in the experimental group were 4.31 ± 0.33 and 1.09 ± 0.12 min, respectively; B: the durations of angina pectoris before and after treatment in the control group were 4.32 ± 0.36 and 2.81 ± 0.27 min, respectively. These results are shown in Figure 1.

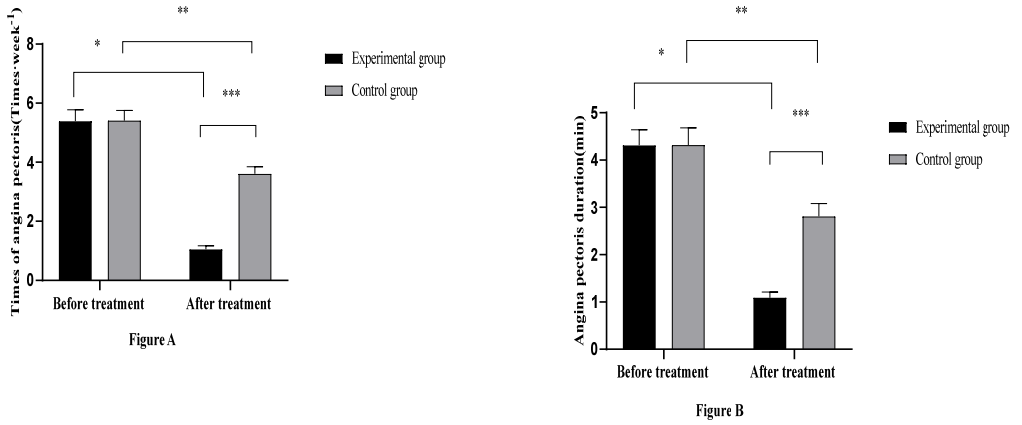

Figure 1: Number and duration of angina pectoris in the two groups (mean ± SD). A: **P* < 0.001, number of angina pectoris before vs number of angina pectoris after treatment in the experimental group; ***p* < 0.001, number of angina pectoris before vs number of angina pectoris after treatment in the control group; ****p* < 0.001 number of angina pectoris in the experimental group vs number of angina pectoris in the control group. B:; **p* < 0.001, duration of angina pectoris before vs duration of angina pectoris after treatment in the experimental group; ** *p* < 0.001, duration of angina pectoris before vs duration of angina pectoris after treatment in the control group; ****p* < 0.001, duration of angina pectoris in the experimental group vs duration of angina pectoris in the control group

PRA level

As shown in Figure 2, after treatment, significantly lower level of panel reactive antibodies (PRA) in the experimental group vs. Control group was observed ($p < 0.05$). The PRA levels of the experimental group before and after treatment were 9.23 ± 1.79 and 2.25 ± 1.13

ng/mL/h, respectively; the PRA levels of the control group before and after treatment were 9.27 ± 1.75 and 5.65 ± 1.18 ng/mL/h, respectively.

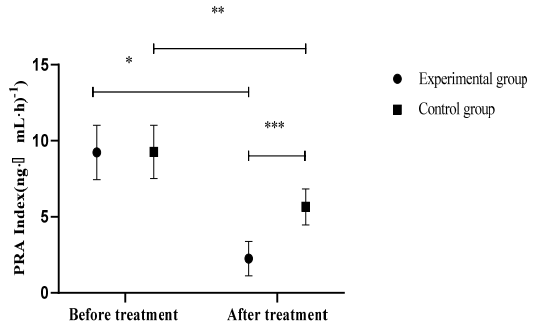

Figure 2: Comparison of PRA levels between the two groups (mean ± SD). *P < 0.001, PRA levels before vs PRA levels after treatment in the experimental group; **p < 0.001, PRA levels before treatment vs PRA levels after treatment in the control group; ***p < 0.001, PRA levels in the experimental group vs PRA levels in the control group

DISCUSSION

Acute myocardial injury (AMI) is characterized by high mortality and high disability, and its pathogenesis is associated with drastic emotional changes, overeating, and external environmental factors [11,12]. Meglumine cAMP produces some clinical effects in the treatment of AMI by increasing myocardial contractility, improving the pumping of the heart, and reducing myocardial oxygen consumption. However, it has been clinically confirmed that monotherapy of AMI with meglumine cAMP does not result in promising curative effect and high safety [13].

Ulinastatin, a beneficial immuno-modulatory drug with a strong inhibitory effect on trypsin, is mostly used to treat and rescue patients with acute circulatory failure. Studies have pointed out that combination of the two drugs yielded a desirable curative effect when used in AMI patients. In addition, hs-CRP, an indicator of serum inflammatory factors, is a non-specific marker that reflects the anti-acute phase of systemic inflammation, and its level is associated with the occurrence, severity, and prognosis of AMI [14]. An important subtype of troponin, cTnI only exists in human cardiomyocytes. When the myocardium is damaged, cTnI is released into the blood circulation in large quantities, resulting in elevation of its serum level. Therefore, cTnI is considered a specific serum marker for evaluation of myocardial damage [15]. Creatine kinase (CK) is used clinically for auxiliary diagnosis of cardio-machine diseases, and high serum level of CK is of diagnostic value for AMI [16].

In the present study, the combination of ulinastatin and meglumine cAMP which was used for treatment of patients in the experimental group, led to decreases in serum indexes and enhancement of immune function, thereby ensuring rapid post-treatment recovery [17].

Aggravated heart failure is attributed to excessive activation of the neuroendocrine system which causes increase in PRA level, leading to secondary damage to cardiovascular tissues. In severe cases, this may even lead to the continuous deterioration of cardiac function. The current study revealed a lower post-treatment level of PRA in the experimental group versus the control group. This indicates that combined treatment with ulinastatin and meglumine cAMP markedly decreased neuroendocrine hormone levels of patients and inhibited further aggravation of the disease. Our study also reported higher total treatment effectiveness and safety profiles in the experimental group vs. the control group. These results are consistent with those reported by other scholars [18].

CONCLUSION

This study has demonstrated that treatment of AMI patients with the combination of ulinastatin and meglumine cAMP leads to reductions in clinical symptoms, with marked efficacy and high degree of safety. It also lowers the serum levels of hs-CRP, cTnI and CK. Thus, this combination treatment is a potentially useful strategy for the management of AMI.

DECLARATIONS

Acknowledgement

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Conflict of interest

No conflict of interest associated with this work

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Hairui Jiang, Liru Liu and Huiying Sui wrote the manuscript

text. Bo Liang and Lingyu Jin prepared Figures and Tables. All authors reviewed the manuscript.

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