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Original Article

Efficacy of metoprolol plus atorvastatin for carotid atherosclerosis and its influence on carotid intima-media thickness and homocysteine level

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Abstract: Objective: To analyze the effects of metoprolol (MET) plus atorvastatin (ATO) on carotid intima-media thickness (IMT) and homocysteine (Hcy) level in carotid atherosclerosis (CAS) patients. Methods: In this retrospective study, 90 patients with CAS admitted to the Hangzhou Ninth People's Hospital between January 2019 and July 2021 were enrolled, including 40 cases (control group, the Con) treated with MET and 50 cases treated with the combination therapy of MET plus ATO (Research group, the Res). The efficacy and related influencing factors were observed and compared. The clinical effects (IMT, plaque score), Hcy level, inflammatory cytokines (ICs; matrix metalloproteinase-9 [MMP-9], high-sensitivity C-reactive protein [hs-CRP]), blood lipid indices (low-/high- density lipoprotein cholesterol [LDL-C/HDL-C], total cholesterol [TC], triglyceride [TG]) and coagulation markers (thrombin time [TT], prothrombin time [PT], activated partial thromboplastin time [APTT], fibrinogen [FIB]) of the two groups were observed and compared. Results: The results identified a statistically higher overall response rate in the Res group. Age, coronary heart disease, cerebral infarction and plaque score were confirmed to be closely related to the efficacy of CAS. In addition, statistically lower post-treatment IMT, plaque score, MMP-9, hs-CRP, LDL-C, TG, TC and FIB while higher PT, TT and APTT were determined in the Res group compared with the pre-treatment values and the Con group. Conclusions: MET plus ATO can significantly improve efficacy, reduce IMT and plaque score of patients with CAS, as well as improve inflammatory factors, blood lipid indices and coagulation markers, for which it deserves clinical promotion.

Keywords: Metoprolol, atorvastatin, carotid atherosclerosis, carotid intima-media thickness, homocysteine

Introduction

The risk of cardiovascular disease, which threatens the life and health of the elderly, increases with age [1, 2]. As a common cardiovascular disease, carotid atherosclerosis (CAS) can progress to ischemic stroke [3]. According to epidemiological data, 12% of patients with moderate CAS are male and 5% are female, while in patients with severe CAS, 3% are male and 1% are female [4]. Previous studies have shown that CAS is initially characterized by an increase in carotid intima-media thickness (IMT), which then gradually deteriorates into atherosclerotic plaques [5]. As an independent predictive risk factor for strokes, IMT can also directly reflect atherosclerosis severity [6]. In addition, homocysteine (Hcy) is also closely related to the progression of CAS, with a known positive correlation with IMT [7]. At present, the treatment of CAS is mainly based on clinical medication, but the current medication strategy has not fully met the treatment needs of patients [8]. For further exploration of therapeutic strategies for this disease and analysis of its impact on clinical outcomes, IMT and Hcy, can provide a theoretical basis for the treatment of CAS.

The pathological mechanisms of CAS have been shown to be related to inflammatory reaction, dyslipidemia and coagulation disorders [9-11]. Metoprolol (MET), a β receptor blocker, can improve heart rate in mice via interfering with the balance of endothelial β-adrenergic receptor-nitric oxide in animal experiments, thereby exerting anti-atherosclerotic effects

[12]. MET is also known to contain atherosclerosis progression and improve vulnerable plaques' stability via inhibiting inflammation and regulating lipids [13]. Drugs are also widely used to treat arrhythmia, abnormal heart rate after heart transplantation, hypercholesterolemia, etc., which is helpful to improve patient prognosis and left ventricular diastolic function, with beneficial effects on reducing IMT [14-16]. While atorvastatin (ATO) is a common statin with lipid-lowering and cardioprotective effects, it can play an anti-inflammatory role in carotid atherosclerotic lesions by down-regulating vascular cell adhesion molecule-1 (VCAM-1) and up-regulating miR-126 [17, 18]. It has also been reported that ATO can improve the coagulation state of the body by reversing the abnormal coagulation indexes, and significantly enhance the endothelial function and thrombofibrinolytic system in patients with cardiac failure [19].

This study mainly analyzes the efficacy of MET plus ATO on CAS patients and its influence on carotid intima-media thickness and Hcy level, aiming at providing effective clinical reference for such patients.

Materials and methods

General data

In this retrospective study, patients (n=90) diagnosed with CAS and treated in the Hangzhou Ninth People's Hospital from January 2019 to July 2021 were enrolled. Among them, 40 cases (24 males and 16 females, mean age: 64.41±11.04 years) in the control group (the Con) received MET treatment. The remaining 50 patients, with a male-to-female ratio of 29:21 and a mean age of (65.20±13.10) years, were assigned to the research group (the Res) and received MET plus ATO therapy. The basic clinical information such as sex and age differed insignificantly between the two groups, indicating comparability ($P > 0.05$). Ethical approval (Approval Number: 2022-000-J036) was been obtained from the Hangzhou Ninth People's Hospital. The enrolled cases (non-gestation or lactation) were all diagnosed with CAS and received MET plus ATO or MET monotherapy [20], with complete medical records and normal cognitive and communication abilities. Patients were excluded if they had severe heart, lung, kidney and other organ diseases, allergies to the study medication, asymptomatic bradycardia or hypotension, stroke, autoimmune diseases, chronic infectious diseases or coagulation dysfunction.

Treatment protocols

The Con: Patients were given Metoprolol Succinate Sustained-release Tablets (JiangXi Revere Biotech, RWE10128) once daily at 47.5 mg initially and then a 23.75 mg increase every 7-14 days until the maximum tolerated dose of 95.0 mg. The treatment lasted for 24 weeks.

The Res group was treated with MET plus ATO. On the basis of the Con, 20 mg Atorvastatin Calcium Tablets (Shenzhen Excellent Biomedical Technology Co., Ltd., 234d) was administered once a night for 24 weeks.

Outcome measures

Efficacy: Marked response: after treatment, the thickness and area of carotid atherosclerotic plaque were significantly improved, with the blood pressure returned to normal. Response: the thickness and area of carotid atherosclerotic plaque were improved, and the blood pressure was basically normal after treatment. Non-response: no improvement in carotid atherosclerotic plaque thickness and area after treatment. The overall response rate was the sum of marked response rate and response rate.

Clinical effects: We evaluated the treatment efficacy by measuring IMT and plaque score. IMT was measured by color Doppler ultrasound (Xuzhou Dawei Metal Chemical Products Co., Ltd., DW-C8) at a frequency of 5.0-10.0 MHz. Bilateral common carotid arteries were scanned before and 24 weeks after medication, and the mean value of IMT was recorded and calculated. The plaque score was measured using the semi-quantitative method to evaluate the severity of CAS, and the evaluation criteria were as follows: 0: no plaque; 1 point: presence of only one plaque with thickness < 2 mm; 2 points: presence of two plaques with thickness < 2 mm or one plaque with thickness > 2 mm; 3 points: presence of two plaques, with at least

Table 1. Patients' baseline data [n (%), mean ± SD]

Factors	n	Control group (n=40)	Research group (n=50)	χ^2/t	P
Gender				0.037	0.848
Male	53	24 (60.00)	29 (58.00)		
Female	37	16 (40.00)	21 (42.00)		
Age (years)				0.020	0.887
< 65	42	19 (47.50)	23 (46.00)		
≥ 65	48	21 (52.50)	27 (54.00)		
Average age (years)	90	64.41±11.04	65.20±13.10	0.305	0.762
Course of disease (years)	90	2.25±0.53	2.34±0.60	0.744	0.459
Coronary heart disease				0.376	0.540
No	44	21 (52.50)	23 (46.00)		
Yes	46	19 (47.50)	27 (54.00)		
Hypertension				0.003	0.955
No	20	9 (22.50)	11 (22.00)		
Yes	70	31 (77.50)	39 (78.00)		
Cerebral infarction				0.321	0.571
No	42	20 (50.00)	22 (44.00)		
Yes	48	20 (50.00)	28 (56.00)		
Diabetes mellitus				0.970	0.325
No	58	28 (70.00)	30 (60.00)		
Yes	32	12 (30.00)	20 (40.00)		
Plaque score (points)				0.436	0.509
< 4	46	22 (55.00)	24 (48.00)		
≥ 4	44	18 (45.00)	26 (52.00)		

one with thickness > 2 mm; 4 points: presence of more than two plaques with thickness > 2 mm.

Inflammatory cytokines (ICs; high-sensitivity C-reactive protein [hs-CRP], matrix metalloproteinase-9 [MMP-9]). Five mL of venous blood from the elbow was collected from each patient before treatment and 24 weeks after medication, and serum was obtained after centrifugation for the determination of MMP-9 and hs-CRP using enzyme-linked immunosorbent assay (ELISA). The operation process strictly followed the instructions of human MMP-9 ELISA kit and human hs-CRP ELISA kit (Shanghai Fuyu Biotech, FY-03502H2, FY-03230H2).

Blood lipid indices (total cholesterol [TC], low-/high- density lipoprotein cholesterol [LDL-C/HDL-C], triglyceride [TG]) and Hcy. The above lipid indices and Hcy were determined with the use of an automatic biochemical analyzer (Dongguan Yimai Electric Light Source Co., Ltd., 5698742).

Coagulation markers (thrombin time [TT], prothrombin time [PT], activated partial thromboplastin time [APTT], fibrinogen [FIB]). These coagulation markers were measured by an automated coagulometer (Beijing STAGO Diagnosis Trading Co., Ltd., 58732).

Statistical processing

SPSS 22.0 was used to perform statistical analysis of the data. Categorical and quantitative variables were denoted by cases/percentages (n/%) and mean ± SEM, respectively. A Chi-square test was used to identify the inter-group difference of categorical data, and a Chi-square continuity correction was applied when the theoretical frequency was less than 5 in the Chi-square test. As to quantitative variables, the independent samples t-test and paired t-test were used to determine the inter-group difference and intra-group difference, respectively. $P < 0.05$ was the threshold for statistical significance.

Results

Comparative analysis of clinical data

The two groups were comparable in clinical data, showing no distinct difference in gender, age, mean age, course of disease, coronary heart disease, hypertension, cerebral infarction, diabetes and plaque score (all $P > 0.05$) (**Table 1**).

Influence of MET plus ATO on efficacy of CAS patients

The treatment efficacy of both cohorts of subjects were evaluated, and it was found that the overall response rate of the Res group was significantly higher than that of the Con group

Table 2. Effect of metoprolol plus atorvastatin on efficacy of arotid atherosclerosis patients [n (%)]

Groups	n	Marked response	Response	Non-response	Overall response rate (%)
Control group	40	16 (40.00)	12 (30.00)	12 (30.00)	28 (70.00)
Research group	50	24 (48.00)	20 (40.00)	6 (12.00)	44 (88.00)
χ^2 value	-	-	-	-	4.500
P value	-	-	-	-	0.034

Table 3. Analysis of related factors influencing efficacy of carotid atherosclerosis patients [n (%)]

Factors	n	Response group (n=72)	Non-response group (n=18)	χ^2	P
Gender				1.652	0.199
Male	53	40 (55.56)	13 (72.22)		
Female	37	32 (44.44)	5 (27.78)		
Age (years old)				5.402	0.020
< 65	42	38 (52.78)	4 (22.22)		
≥ 65	48	34 (47.22)	14 (77.78)		
Course of disease (years)				0.292	0.589
< 3	55	45 (62.50)	10 (55.56)		
≥ 3	35	27 (37.50)	8 (44.44)		
Coronary heart disease				9.349	0.002
No	44	41 (56.94)	3 (16.67)		
Yes	46	31 (43.06)	15 (83.33)		
Hypertension				1.607	0.205
No	20	18 (25.00)	2 (11.11)		
Yes	70	54 (75.00)	16 (88.89)		
Cerebral infarction				8.136	0.004
No	42	39 (54.17)	3 (16.67)		
Yes	48	33 (45.83)	15 (83.33)		
Diabetes mellitus				3.746	0.053
No	62	53 (73.61)	9 (50.00)		
Yes	28	19 (26.39)	9 (50.00)		
Plaque score (points)				7.515	0.006
< 4	46	42 (58.33)	4 (22.22)		
≥ 4	44	30 (41.67)	14 (77.78)		

(88.00% *vs.* 70.00%), with statistical significance ($P < 0.05$) (**Table 2**).

Analysis of related influencing factors of efficacy in CAS patients

The enrolled patients were divided into two groups: response group (n=72) and non-response group (n=18). Further analysis of the clinical data of the two groups showed that there were significant differences in age, coronary heart disease, cerebral infarction and plaque scores ($P < 0.05$) (**Table 3**).

Clinical effects of MET plus ATO in CAS patients

We analyzed IMT and the plaque score of two groups of patients to explore the influence of the two interventions on the clinical outcomes of CAS patients. IMT and plaque score differed insignificantly between the Con and the Res groups before treatment ($P > 0.05$); but the two indexes reduced significantly after treatment ($P < 0.05$), with significantly lower values in the Res ($P < 0.05$) (**Figure 1**).

Influence of MET plus ATO on Hcy in CAS patients

We examined Hcy in both cohorts of CAS patients to explore the impacts of the two treatments on Hcy level. Similarly, no statistical difference was observed in Hcy level between groups prior to treatment ($P > 0.05$). The post-treatment Hcy level reduced markedly in both cohorts, with a significantly lower level in the Res ($P < 0.05$) (**Figure 2**).

Influence of MET plus ATO on ICs in CAS patients

We analyzed the effect of MET plus ATO on inflammatory responses in patients with CAS by detecting two ICs, MMP-9 and hs-CRP. The analysis identified no statistical difference in pre-treatment MMP-9 and hs-CRP levels between the two groups ($P > 0.05$); after treatment, statistically decreased MMP-9 and hs-CRP were observed in both cohorts of patients, with more evident reduction in the Res group ($P < 0.05$) (**Figure 3**).

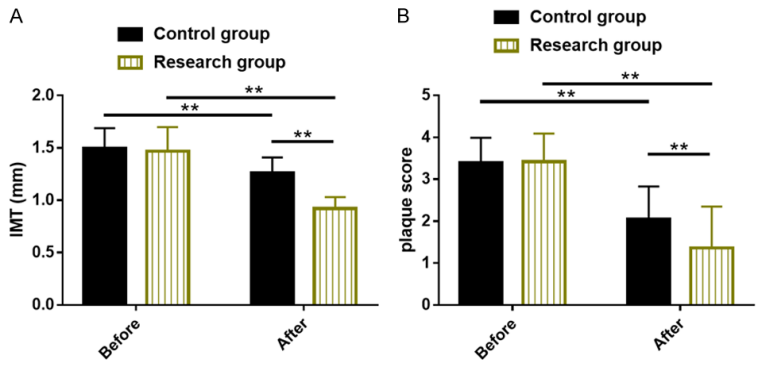

Figure 1. Effect of metoprolol plus atorvastatin on clinical effects of patients with carotid atherosclerosis. A. The post-treatment IMT in the research group was lower than the pre-treatment level and the control group. B. The post-treatment plaque score of the research group was lower than the pre-treatment level and the control group. Note: Compared between the two groups or compared with the value before treatment, $^{**}P < 0.01$. The independent samples t-test was used to analyze inter-group data, and the paired t test was used to analyze intra-group data before and after treatment. IMT, carotid intima-media thickness.

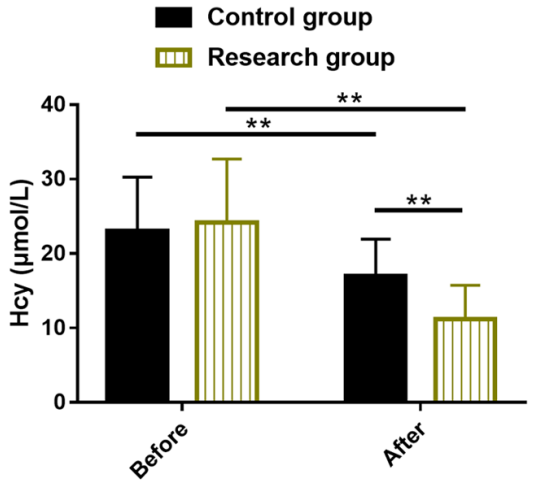

Figure 2. Effect of metoprolol plus atorvastatin on Hcy in patients with carotid atherosclerosis. Note: Compared between the two groups or compared with the value before treatment, $^{**}P < 0.01$. The independent samples t-test was used to analyze inter-group data, and the paired t test was used to analyze intra-group data before and after treatment. Hcy, homocysteine.

Influence of MET plus ATO on blood lipid indices in CAS patients

No significant difference was determined in pre-treatment blood lipid indices between groups ($P > 0.05$), nor were there any notable differences before and after the treatment in the Con group ($P > 0.05$). While in the Res, blood lipid indices differed statistically before and after treatment ($P < 0.05$), with better improvement degree than the Con group ($P < 0.05$) (**Figure 4**).

Influence of MET plus ATO on coagulation markers in CAS patients

The detection results of coagulation markers indicated no statistical difference between the two groups prior to treatment ($P > 0.05$). However, PT, TT and APTT elevated notably in both cohorts after treatment ($P < 0.05$), while FIB decreased ($P < 0.05$). Significant differences were observed in post-treatment coagulation markers between the two groups ($P < 0.05$) (**Figure 5**).

Discussion

CAS is a chronic inflammatory disorder originating from the arterial wall, which is related to the formation of multiple plaques in the artery [21]. CAS can lead to an increased risk of developing cerebrovascular disorders, ischemic heart disease and peripheral vascular diseases, posing a grave threat to human health [22]. Therefore, the research on the treatment strategy of CAS is of great practical implications for the prevention of the disease and the management of such patients.

The common treatment methods for CAS are surgery and drug therapy, among which the surgical options mainly include carotid endarterectomy and carotid artery stenting, while the medication options mainly include statins and β-blockers [23]. However, surgical treatment is associated with a risk of complications and is closely associated with poor outcomes such as increased risk of stroke and death [24]. While statins and β-blockers have been proven to inhibit cardiovascular events and IMT progression, with a positive effect on the treatment of CAS [25]. In this study, the overall response rate in the Res group after combination therapy was obviously higher compared with the Con

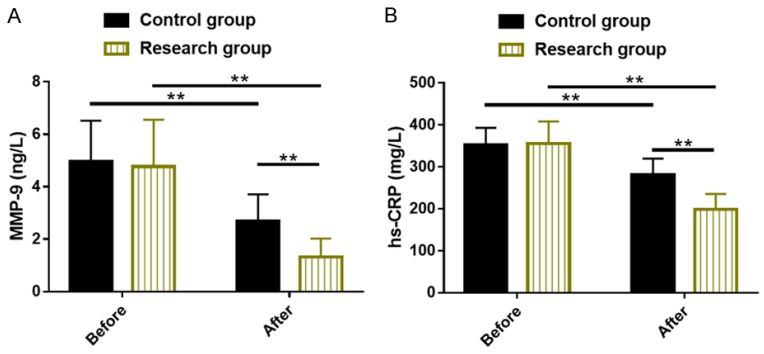

Figure 3. Effect of metoprolol plus atorvastatin on inflammatory factors in patients with carotid atherosclerosis. A. The post-treatment MMP-9 level in the research group was significantly lower than the pre-treatment level and the control group. B. The hs-CRP level in the research group was significantly lower than the pre-treatment level and the control group. Note: Compared between the two groups or compared with the value before treatment, $^{**}P < 0.01$. The independent samples t-test was used to analyze inter-group data, and the paired t test was used to analyze intra-group data before and after treatment. MMP-9, matrix metalloproteinase-9; hs-CRP, high-sensitivity C-reactive protein.

group, indicating that the clinical efficacy of MET plus ATO for CAS is more prominent than MET alone. Further, we analyzed the related factors affecting the efficacy of CAS and found that old age (≥65 years old), coronary heart disease, cerebral infarction, and high plaque score (4 points) were significantly correlated with the treatment non-response of CAS patients. In addition, the IMT and plaque score of the Res group after receiving combined drug therapy reduced markedly and were significantly lower compared with the Con group, suggesting that MET plus ATO can downgrade patients' disease severity. Moreover, the combination therapy was far superior to MET monotherapy in the degree of clinical improvement and the inhibition of Hcy level. Abnormal up-regulation of Hcy level in blood is shown to induce hyperhomocysteine, which is an important inducement for the deterioration of atherosclerosis [26]. Atar et al. [27] confirmed that MET had a potent inhibitory effect on the plasma Hcy level of female patients with hypertension. ATO has been reported to reduce the instability of atherosclerotic plaques by inhibiting endoplasmic reticulum stress in mice with hyperhomocysteine [28]. In the study of Chen et al. [29], ATO significantly suppressed serum Hcy concentration in elderly type 2 diabetic patients complicated with CAS, with a marked effect on plaque stabilization, which is similar to our research results.

In terms of inflammation, blood lipid and coagulation, the improvement effect of MET plus ATO on patients with CAS was found to be significantly better than that of MET monotherapy. Among various ICs that mediate plaque vulnerability processes, MMP-9 is shown to be closely related to plaque instability [30]. Moreover, hs-CRP has a close association with the three-year prognosis of atherosclerosis patients, which can help predict the adverse progression of atherosclerosis [31]. Therefore, MMP-9 and hs-CRP, as typical representatives of ICs, are both related to the deterioration of CAS. Hence, we studied the effects of two intervention methods on MMP-9 and hs-CRP. This study confirmed that the combined treatment intervention has a significant inhibitory effect on MMP-9 and hs-CRP in patients with CAS, and this inhibition was superior in the monotherapy. In the study of Ozova et al. [32], MET combined with ATO alleviated the inflammatory response of patients with ischemic chronic heart failure, which can testify to our findings. As far as blood lipid is concerned, ATO can improve the blood lipid level of obese and hypercholesterolemia patients by repairing mitochondrial ultrastructure in hypercholesterolemia [33]. Atalar et al. [34] reported that ATO can significantly inhibit FIB level and has an anticoagulant effect in treating hyperlipidemic patients with coronary disease.

The innovation of this study lies in the following aspects: first, it confirmed the clinical effectiveness of MET plus ATO in the treatment of CAS from the perspective of efficacy and clinical effects and analyzed the related factors affecting the efficacy. Second, starting from the CAS inducement factor - Hcy level, the impact of two interventions on Hcy level was quantified. Third, based on the blood samples of the subjects, the influence of the two drug therapies on the pathological changes of CAS, such as inflammation, blood lipid and coagulation, was analyzed. The study can be further improved in several ways. First of all, given the small sample

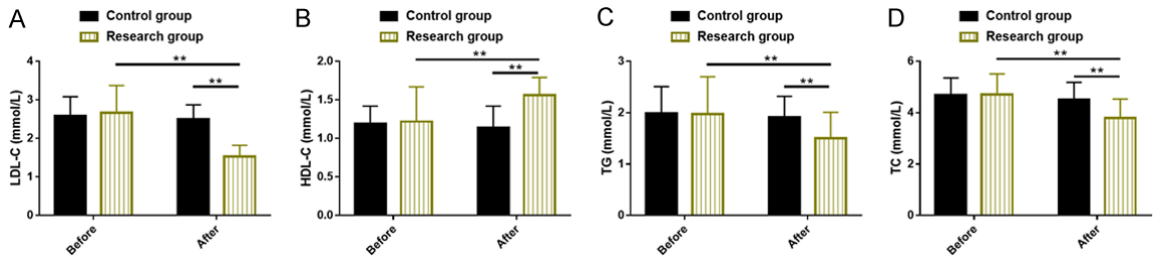

Figure 4. Effect of metoprolol plus atorvastatin on blood lipid indices in patients with carotid atherosclerosis. A. The post-treatment LDL-C level in the research group was lower than the pre-treatment level and the control group. B. The post-treatment HDL-C level in the research group was higher than the pre-treatment level and the control group. C. The post-treatment TG level in the research group was lower than the pre-treatment level and the control group. D. The post-treatment TC level in the research group was lower than the pre-treatment level and the control group. Note: Compared between the two groups or compared with the value before treatment, $^{**}P < 0.01$. The independent samples t-test was used to analyze inter-group data, and the paired t test was used to analyze intra-group data before and after treatment. TC, total cholesterol; LDL-C/HDL-C, low-/high- density lipoprotein cholesterol; TG, triglyceride.

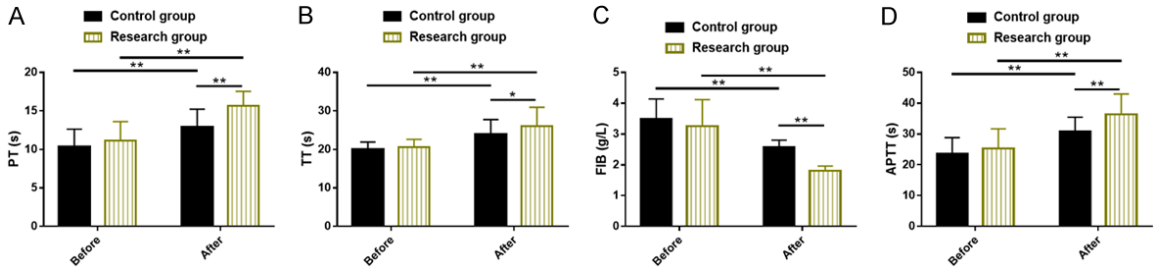

Figure 5. Effect of metoprolol plus atorvastatin on coagulation markers in patients with carotid atherosclerosis. A. The post-treatment PT in the research group increased markedly and was higher versus the control group. B. The post-treatment TT in the research group increased markedly and was higher versus the control group. C. The post-treatment FIB in the research group reduced markedly and was lower versus the control group. D. The post-treatment APTT in the research group increased markedly and was higher versus the control group. Note: Compared between the two groups or compared with the value before treatment, $^{*}P < 0.05$, $^{**}P < 0.01$. The independent samples t-test was used to analyze inter-group data, and the paired t test was used to analyze intra-group data before and after treatment. TT, thrombin time; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen.

size, more patients should be included in future research to improve the accuracy of the conclusions. In addition, it would be better to supplement basic experiments, which will be conducive to further analyzing the therapeutic mechanism of the combination drug therapy in CAS. Finally, prognostic analysis will be helpful to better understand the long-term efficacy of the combination therapy in CAS. The above deficiencies will be gradually addressed to improve the research project.

Collectively, MET plus ATO has a definite clinical effects in the treatment of patients with CAS, which can reduce IMT and inhibit Hcy secretion, and improve blood lipids, inflammation and the coagulation state of patients, providing new insights for the optimization of clinical treatment strategies for such patients.

Disclosure of conflict of interest

None.

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