Effect of butylphthalide soft capsule on the anti-inflammatory effect and plaque stability in patients with ischemic cerebrovascular disease and carotid atherosclerosis

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ARTICLE INFO

Objective: To explore the effect of butylphthalide soft capsule on the serum hs-CRP, MMP-9, and TNF-α in patients with ischemic cerebrovascular disease in order to evaluate the therapeutic effect in the treatment of carotid atherosclerosis. Methods: According to the carotid ultrasound results, the patients were divided into the stable plaque group (control group) and the vulnerable plaque group. The patients in the vulnerable plaque group were randomized into the intervention 1 group and intervention 2 group. The patients in the two subgroups were given bayaspirin and atorvastatin. On this basis, the patients in the intervention 1 group were given butylphthalide soft capsules. The serum hs-CRP, MMP-9, and TNF-α before treatment and 6 months after treatment in each group were detected. The color Doppler ultrasound was used to measure and evaluate IMT, Crouse score, and plaque echo change. Results: The serum hs-CRP, MMP-9, and TNF-α levels before treatment between the two subgroups were significantly higher than those in the control group (P<0.05), but the comparison between intervention 1 group and intervention 2 group was not statistically significant (P>0.05). The serum hs-CRP, MMP-9, and TNF-α levels 6 months after treatment in the two subgroups were significantly reduced when compared with before treatment (P<0.05). The serum hs-CRP, MMP-9, and TNF-α levels after treatment in the intervention 1 group were significantly lower than those in the intervention 2 group (P<0.05). IMT 6 months after treatment in the two subgroups was significantly reduced when compared with before treatment (P<0.05). The reduced degree of IMT after treatment in the intervention 1 group was significantly greater than that in the intervention 2 group (P<0.05). The unstable plaque number after treatment in the intervention 1 group was significantly lower than that in the intervention 2 group (P<0.05). Conclusions: Butylphthalide soft capsule can resist the inflammation, reverse the proliferation of carotid intima, stabilize the vulnerable plaque, and remove the non-atherosclerotic plaque.

1. Introduction

Carotid atherosclerosis (AS) is a pathological process of chronic inflammatory reaction, and is a kind of reaction of blood vessels to the wounding factors[1], in which various cytokines play an important role, while appropriate influence on the expressions of these cytokines probably has a practical and effective therapeutic effect in the treatment of AS[2]. Butylphthalide (NBP, trade name: Enbipu) is a kind of levobutylphthalide extracted from the celery seeds, and has an accurate efficacy in the treatment of ischemic cerebrovascular disease at an acute phase and the cognitive dysfunction[3]. The study is aimed to explore the effect of butylphthalide soft capsule on the serum hs-CRP, MMP-9, and TNF-α in patients with ischemic cerebrovascular disease in...
order to evaluate the therapeutic effect in the treatment of carotid atherosclerosis.

2. Materials and methods

2.1. General materials

A total of 150 patients with ischemic cerebrovascular disease who were admitted in the Third Hospital of Hebei North University and the Department of Neurology of the First People’s Hospital of Zhangjiakou from December, 2014 to January, 2016 were included in the study, among which 100 were male, and 50 were female; aged from 40 to 79 years old. The patients had new-onset cerebral infarction or TIA attack 30 d before inclusion, excluding the intracranial hemorrhagic disease (including hemorrhage after cerebral infarction) by cranial CT and confirmed by cranial MRI, and mRS $\leq 4$ scores. According to the carotid ultrasound results, the patients were divided into the stable plaque group (control group, $n=50$) and the vulnerable plaque group ($n=100$). The patients in the vulnerable plaque group were randomized into the intervention 1 group ($n=50$) and intervention 2 group ($n=50$). The comparison of gender, age, BMI, blood pressure, blood sugar, blood lipid, previous heart disease history, and smoking among each group was not statistically significant ($P>0.05$), but it was comparable. Exclusion criteria: (1) those who were pregnant or at the lactation period; (2) those who had cardiogenic embolism, acute coronary syndrome, non-atherosclerotic vasculitis, hypercoagulation, and hematological system disease; (3) those who were merged with severe arrhythmia, heart failure, liver and renal dysfunction, autoimmune disease, thyroid disease, tuberculosis, and malignant tumor; (4) those who had taken lipid-lowering drugs 4 weeks before admission; (5) those who had severe infection.

2.2. Methods

The patients in the vulnerable plaque group (intervention 1 group and intervention 2 group) were given blood pressure control, fluid infusion, and improvement of bad living habits, such as smoking, alcohol addiction, and high fat diet. The patients in the intervention 1 group were given NBP soft capsule (produced by CSPC NBP Pharmaceutical Co. Ltd, Approval No. H20050299), 0.2 g, 3 times each day, bayaspirin (produced by Bayer, Approval No. J20080078), 100 mg, 1 time each day, and atorvastatin calcium (produced by Beijing Jialin Pharmaceutical Co. Ltd, Approval No. H20093819), 20 mg, qn. The patients in the intervention 2 group were given bayaspirin, 100 mg, 1 time each day, and atorvastatin calcium, 20 mg, qn. Six-month treatment was regarded as one course. During the treatment process, no lipid-lowering drugs and antioxidation drugs were taken.

2.3. Observation indicators

vivid7 color Doppler ultrasound apparatus (produced by GE) was adopted, with transducer frequency of 7.5–10 MHz. IMT of CCA was measured 10 mm from the posterior wall of distal segment of CCA. If AS plaque existed, IMT was measured 10–15 mm from the proximal end of lesions. CCA-IMT values from the bilateral posterior, lateral, and anterior positions were measured, and the average value was recorded. AS plaque number, morphology, echo characteristics, location, and Crouse score in the distal end of bilateral CCA (10 mm from the initial bifurcation of carotid artery), partial bifurcation of carotid body, and initial segment of ICA (10 mm from the bifurcation of carotid artery). Crouse method was used to calculate the carotid plaque score, i.e. Irrespective of the length of each plaque, the maximum thickness of bilateral isolated plaques was added, and Crouse score was obtained. A volume of 3 mL morning fasting venous blood before and after treatment in each group was collected. ELISA was used to detect the serum hs-CRP, MMP-9, and TNF-$\alpha$ levels.

2.4. Statistical analysis

SPSS 17.0 software was used for the statistical analysis. The measurement data were expressed as mean$\pm$SD. The paired $t$ test was used for the intra-group comparison, ANOVA was used for the comparison among each group, among which chi-square test was used for the comparison of enumeration data. $P<0.05$ was regarded as statistically significant.

3. Results

3.1. Comparison of the serum hs-CRP, MMP-9, and TNF-$\alpha$ before and after treatment among each group

The serum hs-CRP, MMP-9, and TNF-$\alpha$ levels before treatment between the two subgroups were significantly higher than those in the control group ($P<0.05$), but the comparison between intervention 1 group and intervention 2 group was not statistically significant ($P>0.05$). The serum hs-CRP, MMP-9, and TNF-$\alpha$ levels 6 months after treatment in the two subgroups were significantly reduced when compared with before treatment ($P<0.05$). The serum hs-CRP, MMP-9, and TNF-$\alpha$ levels after treatment in the intervention 1
group were significantly lower than those in the intervention 2 group \((P<0.05)\) (Table 1).

### 3.2. Comparison of IMT, Crouse score, and plaque number before and after treatment between the two subgroups

Before treatment in the intervention 1 group, 134 plaques were detected, among which 96 were unstable; in the intervention 2 group, 129 plaques were detected, among which 91 were unstable. The comparison of IMT, Crouse, and plaque number before treatment between the two subgroups was not statistically significant \((P>0.05)\). IMT 6 months after treatment in the two subgroups was significantly reduced when compared with before treatment \((P<0.05)\). The reduced degree of IMT after treatment in the intervention 1 group was significantly greater than that in the intervention 2 group \((P<0.05)\). Crouse score after treatment in the two subgroups was significantly reduced when compared with before treatment \((P<0.05)\), but the comparison between the two groups was not statistically significant \((P>0.05)\). The unstable plaque number after treatment in the two subgroups was significantly reduced when compared with before treatment \((P<0.05)\). The unstable plaque number after treatment in the intervention 1 group was significantly lower than that in the intervention 2 group \((P<0.05)\) (Table 2).

### 3.3. Comparison of the adverse reactions

Transaminase was slightly elevated 1 week after medication, and was recovered normal after 4 weeks in the intervention 1 group \((n=3)\) and intervention 2 group \((n=2)\). In the intervention 2 group, 1 had diarrhea. After symptomatic treatment, diarrhea was alleviated, with no severe adverse reactions. The renal function in all patients receiving follow-up was normal. No symptoms, such as myalgia, weakness, fever, nausea, and vomiting occurred.

### 4. Discussion

AS is regarded as an independent risk factor for developing ischemic cerebrovascular disease. Due to the shallow location and easy exploration, the extracranial segment of carotid artery can be served as the window to reflect the systemic AS\([4-6]\). The carotid vulnerable rupture, platelet activation, and thrombosis are mainly involved in the pathogenesis of ischemic cerebrovascular disease\([7]\).

AS plaque is mainly composed of lipid core and fibrous cap, whose stability is mainly dependent on the size of lipid core, the thickness of fibrous cap, and the degree of inflammation degree\([9]\). CRP is an important indicator to detect the inflammation degree, is probably and directly involved in the pathophysiological process of AS, and exists in the whole process of AS, whose level is different in different stages. Hs-CRP, by utilization of hypersensitive method, can more sensitively and accurately detect CRP in order to reflect the inflammation reaction degree of plaques\([10]\). TNF-α is a pro-inflammatory cytokine with wide effects, is mainly produced by the monocytes, lymphocytes, and macrophages in a stress state, can be expressed in the various stages of AS, and plays an important role in the cellular function regulation, immunity, and inflammatory reaction\([11-13]\). The results in the study showed that the serum hs-CRP and TNF-α levels in the vulnerable plaque group were significantly higher than those in the control group \((P<0.05)\), indicating that indicating that the serum hs-CRP level is correlated with the unstable plaques, and higher serum hs-CRP level suggests the vulnerability and rupture of plaques; the serum hs-CRP and

### Table 1

Comparison of the serum hs-CRP, MMP-9, and TNF-α before and after treatment among each group (mean±SD).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>hs-CRP</th>
<th>MMP-9</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>Before treatment</td>
<td>4.70±1.02</td>
<td>77.67±13.49</td>
<td>108.36±11.03</td>
</tr>
<tr>
<td>Intervention 1 group</td>
<td>40</td>
<td>Before treatment</td>
<td>6.06±1.89*</td>
<td>107.66±22.54*</td>
<td>120.32±23.33*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>3.19±0.98*</td>
<td>58.53±17.33*</td>
<td>87.05±19.32*</td>
</tr>
<tr>
<td>Intervention 2 group</td>
<td>50</td>
<td>Before treatment</td>
<td>5.98±2.01*</td>
<td>110.42±23.16*</td>
<td>121.32±20.12*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>3.65±0.90*</td>
<td>73.00±14.52*</td>
<td>103.17±16.85*</td>
</tr>
</tbody>
</table>

*\(P<0.05\), when compared with the control group; \(P<0.05\), when compared with before treatment; \(\Delta P<0.05\), when compared with the intervention 2 group.

### Table 2

Comparison of IMT, Crouse score, and plaque number before and after treatment between the two subgroups (mean±SD).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>IMT</th>
<th>Crous</th>
<th>Unstable plaque number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention 1 group</td>
<td>50</td>
<td>Before treatment</td>
<td>1.52±0.17</td>
<td>7.22±4.58</td>
<td>96(71.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>1.15±0.23*</td>
<td>6.10±3.30*</td>
<td>36(26.9)*</td>
</tr>
<tr>
<td>Intervention 2 group</td>
<td>50</td>
<td>Before treatment</td>
<td>1.58±0.23</td>
<td>7.34±4.22</td>
<td>81(70.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>1.39±0.26*</td>
<td>6.21±3.18*</td>
<td>61(47.3)*</td>
</tr>
</tbody>
</table>

*\(P<0.05\), when compared with before treatment; \(\Delta P<0.05\), when compared with the intervention 2 group.
TNF-α levels 6 months after treatment in the two intervention groups were significantly reduced (P<0.05), and those levels in the intervention 1 group were significantly lower than those in the intervention 2 group (P<0.05), indicating that BNP can inhibit the inflammatory reaction of AS, with a significant therapeutic effect. MMPs can degrade all the components of ECM except polysaccharide, plays an important role in ECM remodeling, can destroy the structure of plaques through degradation of the fibrous cap, and strengthen the instability of plaque to promote its rupture, resulting in thrombosis, and inducing cerebrovascular disease[14]. Among MMPs, MMP-9, with the highest sensitivity and specificity, is mainly distributed in the junction between the normal tissues and plaque, i.e. the place that the vulnerable plaques are the most easy to be ruptured, has a strong degradation effect on ECM, and can accelerate the instability of plaques[15]. Some researches demonstrate that the higher the expression level of MMP-9 in AS plaque, the higher the positive rate of detected microembolus is[16]. It can be seen that MMP-9 with activity can be served as early marker to evaluate the risk of AS rupture. The results in the study showed that MMP-9 level before treatment in the vulnerable plaque group was significantly higher than that in the control group (P<0.05), and the serum MMP-9 level 6 months after treatment in the intervention 1 group was significantly lower than that in the intervention 2 group, indicating that BNP plays an important role in enhancing the stability of vulnerable plaques. The carotid color Doppler ultrasound is currently the effective method to evaluate the atherosclerotic disease, with a higher accuracy rate in detecting the vulnerable plaques, and can directly and repeatedly observe the carotid artery due to the high consistency of observed echo characteristics and the structure characteristics of plaque specimen. The results in the study showed that IMT and unstable plaque number 6 months after treatment in the two subgroups were significantly reduced when compared with before treatment (P<0.05); IMT and unstable plaque number after treatment in the intervention 1 group were significantly lower than those in the intervention 2 group (P<0.05), verifying that BNP can reverse the proliferation of carotid intima, delay the plaque progression, and stabilize the plaques.

In conclusion, butylphthalide soft capsule can resist the inflammation, reverse the proliferation of carotid intima, stabilize the vulnerable plaque, and remove the non-atherosclerotic plaque.

References