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Effects of Valsartan on Restenosis in Patients with Arteriosclerosis Obliterans of the Lower Extremities Undergoing Interventional Therapy: A Prospective, Randomized, Single-Blind Trial

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Statistical Analysis C
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Background: The aim of this study was to further clarify the effects of valsartan on restenosis in patients with arteriosclerosis obliterans of the lower extremities.

Material/Methods: Patients with arteriosclerosis obliterans of the lower extremities undergoing continuous stent implantation in the superficial femoral artery were enrolled and randomly divided into an ARB group and a control group. Patients in the ARB group received valsartan orally in a single-blind manner and were followed up for 6 months. An evaluation was performed based on the criteria for clinical efficacies designed by the Committee of Vascular Disease, Chinese Association of Integrative Medicine. The total clinical effective rate was calculated, and ankle brachial index (ABI) of the patients was assessed. The concentrations of interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) were measured using enzyme-linked immunosorbent assay. The in-stent restenosis of patients was examined by angiography.

Results: One patient in the control group died due to acute cerebral hemorrhage 4 months after enrollment, and 1 patient was lost to follow-up due to acute myocardial infarction during follow-up 5 months after enrollment. Age, sex, Fontaine stage, and underlying diseases were comparable between the 2 groups. Hs-CRP (3.93±1.43) and IL-6 (11.26±2.29) levels were significant different in the ARB group compared with the control group. The postoperative follow-up showed that ABI was 0.98±0.20 in the ARB group and 0.62±0.48 in the control group.

Conclusions: Valsartan inhibited the increase in hs-CRP and IL-6 levels, improved clinical efficacies, increased ABI, and decreased the restenosis rate after the interventional therapy in patients with arteriosclerosis obliterans of the lower extremities.

MeSH Keywords: Endovascular Procedures • Graft Occlusion, Vascular • Peripheral Arterial Disease

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Background

Peripheral arterial diseases (PAD) are common vascular diseases. The prevalence rate of PAD is up to 15.91% in the Chinese elderly population (age over 60 years), and most cases are not diagnosed. The existence of PAD indicates an increase in severity-associated mortality [1]. The current treatment methods include risk factor intervention, drug therapy, surgical intervention, exercise therapy, and treatment with traditional Chinese medicine. The European Society of Cardiology guidelines suggest that stent implantation is the preferred method for mid-length lesions of the femoral artery [2], but postoperative in-stent restenosis can affect clinical outcomes. The 1-year patency rate is 45.1% for the percutaneous transluminal angioplasty of lower-extremity arteries [3]. The 1-year patency rate is 87.3% for self-expanding stent implantation after surgery, and the restenosis after 6 months is 21.9% [4]. Stent implantation can prevent the occurrence of restenosis due to the elastic recoil of blood vessels and vascular remodeling, which inevitably causes damage to the vascular endothelium and leads to vascular damage and rejection response, thereby initiating acute [5] and chronic inflammatory responses of the vascular walls and the release of cytokines and growth factors. The transition and proliferation of smooth muscle cells are activated by multiple signaling pathways to cause restenosis.

Overactivation of the renin-angiotensin-aldosterone system (RAAS) can lead to pathological processes such as elevated vascular resistance and proliferation and fibrosis of myocardial and vascular smooth muscle cells. It can also promote endothelial dysfunction and reduce blood fibrinolysis. Angiotensin II is an important product of RAAS. The activation of angiotensin II and its receptors can produce reactive oxygen species, accelerate vascular endothelial injury, and promote inflammatory cell infiltration. The interaction between angiotensin II and its receptor is closely correlated with in-stent restenosis. Valsartan is an angiotensin-receptor antagonist that can effectively inhibit the proliferation of angiotensin II – induced vascular smooth muscle cells in rats. Its mechanism of action is correlated with regulation of the expression of mitofusin-2 and inhibition of the Ras-Raf-ERK/MAPK signaling pathway [6,7]. Administration of valsartan can increase the levels of hepatocyte growth factor in blood vessels, thus improving myocardial and vascular remodeling [8]. A study found that valsartan-eluting stents could inhibit neointimal hyperplasia in the stent to effectively prevent in-stent restenosis by reducing the collagen deposition and proliferation of smooth muscle cells [9]. Additionally, it has been revealed in recent years that valsartan can inhibit restenosis [9] and need for revascularization surgery [10] by inhibiting inflammatory factors [6–8] and regulating inflammatory responses.

At present, the restenosis rate of endovascular therapy in arteriosclerosis obliterans of lower extremities is high, and some of these patients have to undergo revascularization and amputation after the surgery. Moreover, few studies have reported on the clinical research of drug intervention, and interventional therapy using valsartan for arteriosclerosis obliterans of the lower extremities is rarely reported. This study aimed to evaluate whether the clinical efficacy can be improved by preoperatively administering valsartan to reduce the levels of inflammatory factors and improving in-stent restenosis for patients with stent implantation in the superficial femoral artery.

Material and Methods

Basic data

This was a single-center, open, randomized, and prospective cohort study. We assessed the clinical data of 196 hospitalized patients who underwent stent implantation in the superficial femoral artery due to arteriosclerosis obliterans of the lower extremities and were enrolled from January 2016 to January 2019. The inclusion criteria were as follows: (1) patients satisfied the diagnostic criteria for arteriosclerosis obliterans of the lower extremities [11] and were confirmed to have superficial femoral artery disease; (2) patients with Fontaine stage II–IV, manifesting as intermittent claudication, rest pain, tissue ulcers, and gangrene; (3) patients undergoing stent implantation in the superficial femoral artery, and intraoperative angiography revealing recanalization but without residual restenosis; and (4) patients not using ARBs, β receptor blockers or angiotensin-converting enzyme inhibitors ACEIs. The exclusion criteria were as follows: (1) patients with acute lower limb ischemia; (2) patients with a previous history of stent implantation or artificial bypass grafting of the lower extremities, or who could not tolerate interventional therapy; (3) patients without other ischemic inflammatory diseases such as thromboangiitis obliterans, arteritis, Raynaud's disease, and cold-induced vascular diseases; (4) patients with lesions (stenosis >50% or occlusion) involving the radial artery, middle and distal segments of the popliteal artery, and blood vessels of the calf; and (5) patients who had been taking ARBs. This study was approved by the Ethics Committee of the hospital. The patients and their family members provided informed consent.

The patients were randomly divided into the ARB and control groups, with 98 patients in each group. The single-blind method was used. The patients and their family members agreed to participate in the study. In the ARB group, patients received 20–80 mg valsartan 48 h before the surgery, and interventional therapy for arteriosclerosis obliterans of the lower extremities was performed at an elective date. Moreover, the follow-up was performed by angiography 6 months after stent

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implantation. If blood pressure control of the patients was unsatisfactory during the follow-up period, the dose of valsartan was increased (the maximum dose was 160 mg). In the control group, the blood pressure of patients was controlled with ARBs or ACEIs. The blood pressure of patients in both groups was controlled at about 140/80 mmHg.

The patients with stenosis in the superficial femoral artery of greater than 80% and Fontaine stage III–IV underwent stent implantation by well-trained surgeons specialized in interventional vascular therapy in the hospital according to the angiography of the lower extremities. The interventional method was as follows. The patients were placed in supine position, and surgical drapes were routinely sterilized. Local-infiltration anesthesia was given using 1% lidocaine. The contralateral femoral artery of the affected limb was punctured using Seldinger technique, 3000 U of heparin was intravenously injected, and 1000 U was added every 60 min. The contralateral femoral artery of the affected limb was used as the approach access. If the guidewire could not pass through the lesion, retrograde access was performed from the distal femoral artery of the affected limb. Diagnostic angiography was conducted first to determine the surgical plan. Through the angiography catheter, the tip of a super-smooth guidewire was inserted into the femoral artery, and a 6F vascular sheath was inserted into the proximal end of the lesion. A super-smooth guidewire or V18 guidewire (diameter 0.018 inches and length 300 cm) was inserted into the balloon along the guidewire and passed through the lesion. Balloon dilatation was performed for the lesion, followed by the implantation of a stent. A nickel–titanium self-expanding stent was placed across the 1- to 2-cm lesion at both ends. If the stent was not fully expanded, high-pressure post-expansion was performed using a noncompliant balloon with the diameter of greater than 10% of the reference blood vessels until the stent expanded fully. The criterion of the technical success of stent implantation was <10% postoperative residual stenosis, with no significant dissection or severe complications related to the surgery. The follow-up was continued for 6 months, and angiography of the lower extremity artery was performed. In-stent restenosis was defined as the state when the diameter of restenosis after stent implantation (inside the stent or at the edge of the stent) by angiography was ≥50%; new proliferative lesions 5 mm outside the edge of the stent were also considered to be stent-related restenosis.

Criteria for clinical efficacy [12]: Clinical efficacies were determined based on the criteria of the Committee of Vascular Disease, Chinese Association of Integrative Medicine in October, 1995. Cure: The clinical symptoms of the lower extremities basically disappeared. The wounds of the limbs were completely healed, and the disorder of blood circulation and rheography of the end of the limbs improved significantly. The walking speed was 100–120 steps/min, and walking could be continued for about 1000 m. Significantly effective: The clinical symptoms improved significantly; the wounds of the limbs healed or almost healed; the disorder of blood circulation and rheography of the ends of limbs improved; the walking speed was 100–120 steps/min, and walking could be continued for about 500 m. Effective: The clinical symptoms were alleviated; the wounds of the limbs were almost healed or shrank; the disorder of blood circulation and rheography of the ends of the limbs improved; the walking speed was 100–200 steps/min, and walking could be continued for about 300 m. Ineffective: The symptoms and signs did not improve, or the disease condition progressed after the treatment, and even amputation occurred. The total effective rate=(1–ineffective/total cases) %.

Measurement of ankle brachial index (ABI): An 8-MHz Doppler blood flow probe (Nippon Forest Electric Co.; instrument model: ES21000SP) was used to measure ABI; the balloon of the sphygmomanometer cuff was 10 cm in width and 40 cm in length. The systolic blood pressure of the bilateral upper limbs and the ankle (posterior tibial artery or dorsal artery) was measured in a standard supine position. The highest systolic blood pressures of the upper limbs and the ankle were used. ABI was the ratio of the highest systolic blood pressure of the posterior tibial artery or dorsal artery to the highest systolic blood pressure of bilateral upper limbs.

Detection of high-sensitivity C-reactive protein (hs-CPR) and interleukin-6 (IL-6) levels in plasma: Excluding the patients with infectious diseases, all other patients had 10 mL of blood drawn in the fasting state on the morning before the surgery and 6 months after the surgery. Subsequently, the blood was centrifuged at 3000 rpm for 10 min. The serum was extracted and placed in tubes, which were then stored in a freezer at –70°C. The serum hs-CRP and IL-6 levels were tested using an automatic biochemical analyzer (Beckman Coulter AU5800 series, Beckman Coulter Co., USA).

Statistical analysis: Data were analyzed using IBM SPSS STATISTICS 23.0 SPSS23.0 software. Continuous data were represented by X±standard deviation. (1) Comparison of baseline data: The ages of the 2 groups were compared with the 2 independent-samples *t* test, while data on sex, staging, and underlying diseases were compared using the chi-square test. (2) The clinical efficacies of the groups were compared using the Mann-Whitney *U* test. (3) The ABI and the levels of hs-CRP and ABI were compared between the 2 groups using the paired *t* test. (4) Restenosis was compared using the chi-square test. All the tests were bilateral, and α=0.05 was set as the statistically significant level.

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Results

A total of 196 patients with arteriosclerosis obliterans of the lower extremities, who underwent stent implantation in the superficial femoral artery in Cangzhou Hospital of Integrated TCM-WM, Hebei, from January 2016 to January 2019, were included. The patients were randomly divided into the ARB and control groups. The mean interval from the time after interventional therapy to the follow-up examination of angiography was 183±42 days. In the control group, 1 patient died 4 months after enrollment due to acute hemorrhage, and 1 patient lost to follow-up 5 months after enrollment due to acute myocardial infarction. Data were collected for statistical analysis from the initial stent implantation for arteriosclerosis obliterans of the lower extremities to angiography after 6 months of follow-up. After admission, age, percentage of male patients, history of hypertension, history of coronary heart disease, smoking history, glycosylated hemoglobin level, and clinical Fontaine stage before the surgery, as well as number of patients with stent length of greater than 15 cm after interventional therapy, were not statistically significant ($P>0.05$), which were comparable (Table 1).

Clinical efficacies

In the ARB group, 21 cases (21.4%) were cured, 49 (50.0%) were significantly effective, 25 (25.5%) were effective, while 3 (2.7%) were ineffective. The total effective rate was ineffective/cured+significantly effective+effective%, which was 97.95%. In the control group, 13 patients (13.5%) were cured, 24 (25.0%) were significantly effective, 44 (45.8%) were ineffective, while 15 (15.6%) were ineffective. The total effective rate was ineffective/cured+significantly effective+effective%, which was 84.37%. The differences between the 2 groups were statistically significant ($P<0.05$) (Table 2).

Comparison of restenosis

Six months after the surgery, the restenosis rate was 10.2% in the ARB group and 29.2% in the control group, with a statistically significant difference ($P<0.05$) (Table 3).

Comparison of hs-CRP and IL-6 levels in plasma and ABI

Hs-CRP decreased in both groups. Six months after the surgery, the hs-CRP level decreased from (9.60±2.56) before surgery to (3.93±1.43) after surgery in the ARB group, while it decreased from (10.31±3.12) before surgery to (7.27±1.67) after surgery in the control group. The difference between the 2 groups 6 months after valsartan treatment was statistically significant ($P<0.05$). The IL-6 level decreased in both groups: from (26.45±5.23) before surgery to (11.26±2.29) after surgery in the ARB group, and from (27.12±3.12) before surgery to (16.74±1.90) after surgery in the control group. The IL-6 level

Table 1. Comparison of baseline data between the 2 groups.

	ARB group (98 patients)	Control group (96 patients)	*P*
Age	53.1±6.2	55.1±8.3	0.347
Female sex	74	71	0.804
History of hypertension	80	76	0.665
Smoking history	57	62	0.359
Coronary heart disease	35	42	0.253
Glycated hemoglobin	6.1±1.2	6.0±1.5	0.725
Clinical Fontaine stage III	68	69	0.704
Stent length >15 cm	20	15	0.386

$P<0.05$, compared with the control group.

Table 2. Comparison of the clinical efficacies between the 2 groups.

	Cases	Cure	Significantly effective	Effective	Ineffective	Total effective rate	χ^2	*P*
ARB group	98	21.4% (21)	50.0% (49)	25.5% (25)	2.7% (3)	97.95%	9.094	0.003
Control group	96	13.5% (13)	25.0% (24)	45.8% (44)	15.6% (15)	84.37%		

$P<0.05$, compared with the control group.

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Table 3. Comparison of restenosis between the 2 groups.

	ARB group (98 patients)	Control group (96 patients)	χ^2	*P*
Restenosis rate	11.22% (11)	30.21% (29)	10.678	0.001

P<0.05, compared with the control group.

Table 4. Comparison of ABI and the levels of hs-CRP and IL-in the 2 groups.

		No. of patients	Before the surgery	6 months after the surgery	*t*	*P*
hs-CRP, mg·L^{-1}	ARB group	98	9.60±2.56	3.93±1.43	–9.780	0.001
	Control group	96	10.31±3.12	7.27±1.67		
IL-6, Ng·L^{-1}	ARB group	98	26.45±5.23	11.26±2.29	–3.420	0.000
	Control group	96	27.12±3.12	16.74±1.90		
ABI	ARB group	98	0.61±0.59	0.98±0.20	6.230	0.001
	Control group	96	0.58±0.71	0.62±0.48		

P<0.05, compared with the control group.

was significantly different after 6 months of valsartan treatment (*P*<0.05). After 6 months of follow-up, ABI was 0.98±0.20 in the ARB group and 0.62±0.48 in the control group, and the difference was statistically significant (*P*<0.05) (Table 4).

Discussion

The present study demonstrated that the administration of valsartan before interventional therapy for patients with arteriosclerosis obliterans of the lower extremities could improve postoperative clinical efficacies. Moreover, ABI improved significantly compared with the control group. After excluding infectious factors, serum hs-CRP and IL-6 levels 6 months after the surgery in the ARB group were significantly reduced compared with that in the control group. Also, restenosis in the ARB group was significantly lower than that in the control group, indicating that valsartan partially improved the restenosis rate, improving the poor prognosis of patients with arteriosclerosis obliterans of the lower extremities and reducing re-interventional therapy and amputation to some extent.

Mechanical injury in angioplasty can activate the renin-angiotensin system, increase the inflammatory cytokine levels in targeted atherosclerotic plaques, and aggravate impaired targeted blood vessels and systemic atherosclerosis, leading to acute thrombosis and vascular remodeling. It also elevates the restenosis rate, resulting in revascularization or amputation for some patients. A study showed that valsartan could inhibit atherosclerosis, reduce plaque burden in atherosclerotic vessels [13], and increase fibrous cap thickness and collagen content in plaques, leading to a decrease in plaque vulnerability [14] and thus inhibiting the expression of matrix metalloproteinase-9 after stent implantation [9]. Valsartan could promote a decrease in serum monocyte chemoattractant protein-1 (MCP-1). It also inhibited the expression of peroxisome proliferator–activated receptor γ (PPARγ) in monocytes [15], which stabilizes plaques, causes anti-vascular smooth muscle proliferation and anti-inflammation [16,17], prevents cardiovascular remodeling [16] and intimal hyperplasia [18], reduces the area of new membranes [13], reduces the incidence rate of in-stent restenosis, and reduces the revascularization rate [19]. The present study confirmed that the oral administration of valsartan from before surgery to 6-month follow-up could reduce the release of inflammatory factors, reduce restenosis, and improve clinical prognosis for patients with arteriosclerosis obliterans of the lower extremities who underwent stent implantation in the superficial femoral artery.

This study has the following limitations: (1) The sample size was small, and the study was a single-blind experiment, not a double-blind experiment. (2) The dose of valsartan could not be well controlled, which was based on the blood pressure, and different doses of *valsartan* might have affected the results. (3) The follow-up time was short, and the long-term clinical efficacies of the patients could not be evaluated. During the 6 months of follow-up, the results showed that valsartan improved the restenosis rate and the short-term efficacies compared with the control group. Future studies should explore the mechanism of valsartan in preventing restenosis after endovascular treatment for patients with arteriosclerosis obliterans of the lower extremities. They should also investigate whether

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endovascular treatment can improve middle- and long-term clinical efficacies of patients with arteriosclerosis obliterans of the lower extremities.

Conclusions

In summary, the oral administration of valsartan in this study reduced the restenosis rate and improved clinical prognosis. This study provides a better idea for use of restenosis. However, multiple mechanisms and long-term clinical efficacies of valsartan in preventing in-stent restenosis should be further investigated for patients with arteriosclerosis obliterans of the lower extremities.

Conflict of interests

None.

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