Drug-Eluting Stent Implantation after Percutaneous Transluminal Angioplasty decreases Restenosis Incidence and Inflammatory Reaction in Patients with Lower Extremity Arterial Disease

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Abstract: Lower extremity arterial disease (LEAD) is considered as a common cause resulting the narrowing in the vessels of the lower limbs. This study investigated effect of drug-eluting stent (DES) implantation after percutaneous transluminal angioplasty (PTA) on restenosis incidence in patients with LEAD. The patients with LEAD in control group received PTA alone, and the patients in intervention group received PTA and DES implantation. Skin temperature, transcutaneous oxygen tension (TcPO2), ankle brachial index (ABI), recurrence rate, total response rate, ulcer cure and improvement rates and restenosis incidence 6 months and 12 months after treatment were compared. Clinical symptoms, signs, and foot ulcer condition before and after treatment were compared. Enzyme-linked immunosorbent assay (ELISA) was used to detect the level of like interleukin 6 (IL-6), tumor necrosis factor α (TNF-α) and C-reactive protein (CRP) 3 d and 6 months. Six months after treatment, the patients in intervention group showed increased TcPO2 and ABI and ulcer cure rate but decreased restenosis incidence, and 12 months after treatment, the patients in intervention group exhibited increased skin temperature, TcPO2 and ABI but decreased recurrence rate and restenosis incidence. Moreover, compared with the control group, total response rate, symptoms, signs and foot ulcer condition were increased, but the levels of IL-6, TNF-α and CRP decreased 3 d and 6 months in the intervention group. The total effective rate of restenosis after LEAD intervention was associated with treatment regimen, Fontaine staging, and Hb A1c. Collectively, DES implantation after PTA decreases restenosis incidence and inflammatory reaction in LEAD patients compared with PTA alone.

Keywords: percutaneous transluminal angioplasty; drug-eluting stent implantation; lower extremity arterial disease; restenosis; inflammatory reaction

1. Introduction

Lower extremity arterial disease (LEAD) is a disease which causes patients lower functional capacity [1]. LEAD is one of the complications of diabetes, which damages the peripheral arteries via multiple ways, and patients with diabetes more than 50 years showed 16.9–23.8% prevalence of LEAD in China [2]. LEAD has been a heavy burden for patients, because it has been reported that for patients with LEAD undergoing amputation in China, the average duration of hospitalization was 26 d and the average charge was 14,906 yuan in 2014 with only a survival rate of only 25% over 10 years [3]. LEAD is also related with cerebral disease, coronary disease (CAD) and renal artery disease [4]. Patients with LEAD often suffer from intermittent claudication, rest pain even gangrene [5,6]. Identified risk factors for the onset and progression of LEAD include ageing, cigarette smoking, ethnicity, increased levels of inflammatory markers, obesity and homocysteinaemia [7]. Inflammatory cytokines like interleukin 6 (IL–6), tumor necrosis factor α (TNF-α) and C-reactive protein (CRP) are promising blood biomarkers in cardiovascular disease [8,9]. In addition, metabolic syndrome was found to be a predisposing reason for LEAD [10].

For patients with asymptomatic disease or intermittent claudication, exercise and optimal medical management, such as antiplatelet agents are main therapies [11]. At present, percutaneous transluminal angioplasty (PTA) is usually the primary choice of revascularization for most patients with LEAD in China [12], which is able to expand the location of the stenosis and occlusion for recanalization by using a balloon catheter [13]. However, PTA also presents some disadvantages, such as a higher restenosis incidence [14]. Also, a larger minimal stent area with PTA brought better results in post procedural angiography and stent restenosis in the long-term [15]. Patients with occlusive arterial disease within the coronary circulation, drug eluting stents (DES) is the accepted gold standard [16]. Besides, a previous study has proved that the combination of DES implantation and balloon dilatation may improve safety [17]. A design of DES coating to
anti-inflammatory and anti-thrombotic reactions could help patients gain superior long term patency compared with bare metal stents and percutaneous transluminal angioplasty [18]. Kubo S et al. found that compared with balloon angioplasty, DES implantation was more effective in reducing recurrent in-stent restenosis rate and the revascularization incidence [19]. However, DES still needs to be ameliorated because its compression and recoil may increase restenosis incidence [20,21]. Therefore, we conducted this experiment to investigate the effect of DES expansion adjuvant with PTA on restenosis incidence and levels of IL-6, TNF-α and CRP in patients with LEAD.

2. Material and Methods

2.1. Ethics Statement

This experiment was approved by the ethics committee of China-Japan Union Hospital of Jilin University. Besides, all subjects voluntarily took part in the experiment and all of them signed informed consents.

2.2. Subjects

Seventy-nine patients with LEAD who were admitted in China-Japan Union Hospital of Jilin University from July 2014 to July 2016 were enrolled. They were 48 males and 31 females aging from 40 to 71 years old with mean age of 54.5 ± 9.2 years old. The inclusion criteria were as follows: patients who voluntarily accepted DES implantation and PTA; patients with unobstructed distal outflow tract of the diseased artery (or at least one of the three branches of knee is unobstructed); patients with main vascular lesion at proximal portion of inferior genicular artery, including peroneal artery, posterior tibial artery, anterior tibial artery, and tibiofibular artery with or without superficial femoral artery and iliac artery diseases; patients with physical condition meeting the need for DES implantation or PTA. The exclusion criteria were as follows: patients with poor compliance to take medicine as doctors’ instructions; patients with both severe mental illness and cardio-cerebrovascular diseases; patients with severe renal inadequacy, hepatic insufficiency and cardiac insufficiency at the same time. According to the Fontaine classification system, stages of LEAD include stage I: asymptomatic PAD (without symptoms but objectively diagnosed); stage II: intermittent claudication; stage III: rest pain; stage IV: ulcersations and gangrene [22]. All patients were divided into intervention group (38 patients) and control group (41 patients) on the basis of treatment regimen patient received, followed by analysis of their baseline characteristics and blood biochemical indicators including high-sensitivity C-reactive protein (hs-CRP), uric acid (UA), urate transporter (UAT), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum total cholesterol (TC), and glycated haemoglobin A1c (HbA1c).

2.3. Treatment Regimens

Patients in the control group were treated with the PTA alone while the intervention group was treated with PTA supplemented with DES implantation. EXCEL (JW Medical Systems, Weihai, Shandong, China) was adopted during the DES implantation. Lower extremity arterial stenting was carried out by the experienced specialists according to the standards, and the implanted stent totally covered lesions. After satisfactory anesthesia, improved Seldinger technique was used to place the stent into arterial sheath by antegrade puncture from arteria femoralis. The proximal vessels of lesions were reached with the help of guidance of 4 F catheter with 0.889 mm super-slip guide wire, and digital subtraction angiography was used to define the length, location, distal outflow tract, occlusion degree and collateral circulation of the lesions. When patients were with occlusion or stenosis superior genicular vessel, the stent placement or PTA was performed according to the patients’ condition, and then the DEEP balloon was used for dilatation under the knee lesions. Sirolimus coated bare stent (domestic Firebird) was implanted in the proximal trunk of the diseased artery (the initial segment of the tibiofibular trunk and the arteria tibialis anterior). The procedures of DES implantation in the intervention group were the same as that in the control group. After DES implantation, diver catheter combined with 0.356 mm guide wire was used to pass through the occluded and stenosis vessels under the guidance of road map. In this process, the guide wire was required to outstrip the lesions, and the PTA was carried out after DAS confirmed no mistakes. Criteria of a successful lower extremity arterial intervention were that the restenosis incidence of postoperative diseased vascular remnants was less than 30%, and patients had not serious complications such as angiorrhaxis, thrombopoiesis, local vascular dissection and angioneoplasm.

2.4. Enzyme-Linked Immunosorbent Assay (ELISA)

Elbow venous blood (4 mL. each time for each patient) was collected from each patient admitted in our hospital at the second morning or before acute interventional therapy, 3 d after treatment, and 6 months after treatment, respectively. The collected blood was centrifuged at 3000 r/m for 10 min to isolate serum and plasma, and reserved in a refrigerator. ELISA was used to detect levels of inflammatory factors in the serum including IL-6 (ab178013, Abcam, Cambridge, UK), TNF-α (ab181421, Abcam, Cambridge, UK) and CRP (ab99995, Abcam, Cambridge, UK). The procedures were strictly in accordance with the kit instructions (Beijing North Biotechnology Research Institution, Beijing, China; Dade
Behring, Deerfield, USA). Carbonate coating buffer (pH 9.6) was used to dilute the antigen to a concentration of 1–10 μg/mL, and each well was added with 0.1 mL antigen for incubation overnight at 4°C. The next day, the wells were added with 1 mL diluted supernatant, and then incubated at 37°C for 1 h. The blank, negative and positive wells were set, added with 1 mL fresh diluted enzyme labeled second antibody (Abcam, Cambridge, UK), incubated for 35 - 60 min at 37°C and washed with ddH2O (PER 018-1, Beijing Dingguo Changsheng Biotechnology Co., Ltd, Beijing, China). The wells were added with 0.1 mL temporary configured 3,3’,5,5’-Tetramethylbenzidine (TMB) (EL0001, InnoReagents, Zhejiang, China) substrate solution, incubated for 10–30 min at 37°C and added 50 μL of stop buffer to stop developing. Value of optical density (OD) was measured at the wavelength of 450 nm within 20 min.

2.5. Follow-up

All patients were regularly followed-up at outpatient department so that the researchers can get the latest information about the disease progression and symptoms of patients and inform the patients of review time. Six months and 12 months after treatment, all patients were subjected to computed tomography angiography (CTA) in lower extremity to determine whether they had restenosis. According to CTA, when diameter stenosis within or within 5 mm range of the stent were more than 50%, the occlusion, restenosis, hemorrhage bleeding and ulcers were recorded, and the total response rate and restenosis incidence of patients were calculated. During the last follow-up, clinical symptoms, signs, and foot ulcer condition were asked, observed, and scored (7–35 points). Skin temperature in lesions was classified as normal (5 points); sometimes cold (4 points); continue cold under normal dress but relieve after strengthening local warming (3 points). Pain in lesions was scored as no pain (5 points); pain, intermittent claudication or burning pain after physical activity (4 points); intermittent pain under quiescent condition (3 points); sustainable pain not affect sleep under quiescent condition (2 points); unbearable persistent pain affect sleep under quiescent condition (1 point). Skin colors in lesions were divided into normal color (5 points); intermittent pale or greenish yellow (4 points); sustainable pale or greenish yellow (3 points); cyanosis (2 points); atropurpureus or puce (1 point). Pulsion status of dorsalis pedis and tibialis posterior included normal pulsation (5 points); weakened pulsation for one of arteries (4 points); weakened pulsation for both two arteries (3 points); no pulsation for one of arteries (2 points); no pulsation for both arteries (1 point). Depth of ulcer was classified into no ulcer (5 points); superficial ulcer not reaching muscular layer (4 points); deep ulcer reaching muscular layer but not reaching tendon (3 points); ulcer reaching tendon but not reaching bone or joint (2 points); ulcer reached bone or joint even gangrene (1 point). Areas of ulcer was classified into crustosus healed ulcer (5 points); ulcer diameter < 1 cm or healing area < 80% (4 points); ulcer diameter from 1 cm to 3 cm or healing area from 50–80% (3 points); ulcer diameter from 2 cm to 5 cm or healing area from 20–50% (2 points); ulcer diameter > 5 cm or healing area < 20% (1 point). Infectious condition was classified as no local red swelling (5 points); slight local red swelling (4 points); visible local red swelling (3 points); serious local red swelling (2 points); local red swelling along with a large number of purulent secretion (1 point). Higher points a patient got, better conditions the patient had improved. The score was decided by at least 2 senior doctors together. According to the standard of the Guidance Principle of the Clinic Research of New Traditional Chinese, curative effects were classified as effective (cases %) (accumulate points decreased by ≥ 70.0% after treatment), valid (cases %) (accumulate points decreased by ≥ 30.0% but < 70.0% after treatment), invalid (cases %) (accumulate points decreased by < 30% after treatment) and aggravating (cases %) (accumulate points increased by ≥ 30.0% after treatment). Total effective rate (cases %) = effective cases + valid cases/total cases. Skin temperature, transcutaneous oxygen tension (TePO2), ankle brachial index (ABI), recurrence incidence, ulcers and the incidence of restenosis in patients in the control group and the intervention group were compared 6 months after treatment and 12 months after treatment, respectively. If patients were not able to review at our hospital because of hard physical condition and inconvenient transportation, they were return visited and reviewed in their local hospital. The results of the review were asked by telephone. Patients who finished the clinical observation were asked about the physical condition and disease progress monthly by telephone and asked for return visits.

2.6. Statistical Analysis

All the data analysis was processed by applying SPSS 18.0 statistical software (IBM Corp. Armonk, NY, USA). Measurement data in accordance with normal distribution were presented as mean standard ± deviation. The unpaired t-test was used for comparison between two groups and the paired t-test for comparison among groups before and after treatment. Enumeration data were expressed as a percentage or rate, and comparison between two groups was analyzed by the χ2 test. The factors influenced the total effective rate of restenosis after LEAD intervention were analyzed by Logistic regression analysis. p < 0.05 was indicative of statistical significance.

3. Results

3.1. Baseline Characteristics of Included Patients

Baseline characteristics and blood biochemical indicators in the control and intervention groups (Table 1) were
compared. There was no significant difference among gender, age, smoking, disease history, complication with diabetic, complication with hypertension, complication with coronary heart disease, complication with hyperlipidaemia, ABI, Fontaine stages and blood biochemical indicators (hs-CRP, UA, UAT, HDL, LDL, TC, HbA1c) (all \(p > 0.05\)). Multiple vessel lesions were more common in the control and intervention groups, with long lesions and significant calcification. Single or two target lesion arteries was successfully intervened with PTA. Comparison of angiographic baseline data and PTA intervention between the intervention group and the control group showed no significant difference (\(p > 0.05\)) (Table 2), suggesting the successful PTA intervention.

### Table 1. Baseline characteristics and blood biochemical indicators in the case group and the control group.

| Clinicopathological factors | Intervention (n = 38) | Control (n = 41) | \(\chi^2\) | \(P\) |
|-----------------------------|-----------------------|-----------------|-----------|------|
| Gender (%)                  |                       |                 |           |      |
| Male                        | 22 (57.9)             | 26 (63.4)       | 0.252     | 0.616|
| Female                      | 16 (42.1)             | 15 (36.6)       |           |      |
| Age (%)                     |                       |                 |           |      |
| ≤ 50 years                  | 14 (36.8)             | 16 (39.0)       | 0.04      | 0.842|
| > 50 years                  | 24 (63.2)             | 25 (61.0)       |           |      |
| BMI (kg/m\(^2\))           | 24.37 ± 3.19          | 23.84 ± 2.76    | 0.791     | 0.431|
| Smokers                     | 16 (42.1)             | 15 (36.6)       | 0.502     | 0.616|
| Systolic blood pressure (mmHg) | 136 ± 9.82          | 137 ± 8.60      | 0.482     | 0.631|
| Diastolic blood pressure (mmHg) | 88 ± 5.27             | 87 ± 7.37       | 0.689     | 0.493|
| Disease history (%)         |                       |                 |           |      |
| ≤ 1 year                    | 20 (52.6)             | 20 (48.8)       | 0.117     | 0.732|
| > 1 year                    | 18 (47.4)             | 21 (51.2)       |           |      |
| Complications (%)           |                       |                 |           |      |
| Diabetes                    | 14(36.8)              | 17(41.5)        | 0.177     | 0.674|
| Hypertension                | 20(52.6)              | 25(61.0)        | 0.56      | 0.454|
| Coronary heart disease      | 16(42.1)              | 14(34.1)        | 0.53      | 0.466|
| Hyperlipidemia              | 20(52.6)              | 23(56.1)        | 0.096     | 0.757|
| Ankle brachial index        | 0.37 ± 0.09           | 0.34 ± 0.08     | 1.568     | 0.121|
| Fontaine stages (%)         |                       |                 |           |      |
| II stage                    | 5 (13.2)              | 5 (12.2)        | 0.635     | 0.728|
| III stage                   | 24 (63.2)             | 23 (56.1)       |           |      |
| IV stage                    | 9 (23.7)              | 13 (31.7)       |           |      |
| Artery lesion site          |                       |                 |           |      |
| Iliac arteries              | 9 (23.7)              | 8 (19.5)        | 0.206     | 0.902|
| Femoropopliteal artery      | 23 (60.5)             | 26 (63.4)       |           |      |
| Inferior knee arteries      | 6 (15.8)              | 7 (17.1)        |           |      |
| hs-CRP (mmol/L)             | 3.18 ± 0.46           | 2.97 ± 0.58     | 1.774     | 0.08 |
| UA (μm/L)                   | 315.71 ± 30.11        | 306.90 ± 27.56  | 1.358     | 0.179|
| UAT (ng/ml)                 | 185.23 ± 15.64        | 182.71 ± 17.45  | 0.674     | 0.502|
| HDL (mmol/L)                | 1.46 ± 0.39           | 1.28 ± 0.48     | 1.821     | 0.723|
| LDL (mmol/L)                | 2.42 ± 0.57           | 2.35 ± 0.43     | 0.619     | 0.538|
| TC (mmol/L)                 | 4.94 ± 0.88           | 4.70 ± 1.05     | 1.096     | 0.276|
| HbA1c (%)                   | 7.56 ± 1.24           | 8.04 ± 1.39     | 1.615     | 0.11 |

Note: BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; UA, ursolic acid; UAT, urate transporter; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, serum total cholesterol; HbA1c, glycated haemoglobin A1c.
Data were expressed as mean ± standard derivation.

**Table 2.** Angiographic baseline data and PTA intervention in the case group and the control group.

| Indicators                        | Intervention (n = 38) | Control (n = 41) | \( \chi^2/t \) | \( P \) |
|-----------------------------------|----------------------|------------------|---------------|--------|
| Lesion artery (%)                 | Single               | 18 (47.37%)      | 19 (46.34%)   | 0.896  |
|                                  | Two                  | 8 (21.05%)       | 12 (29.27%)   | 0.639  |
|                                  | Three                | 12 (31.58%)      | 10 (24.39%)   |        |
| Artery diameter (mm)              | 4.97 ± 1.00          | 4.84 ± 0.72      | 0.667         | 0.507  |
| Lesion diameter (mm)              | 0.92 ± 0.11          | 0.97 ± 0.13      | 1.838         | 0.07   |
| Lesion length (cm)                | 9.34 ± 1.28          | 9.61 ± 1.14      | 0.992         | 0.325  |
| Intervention of lesion artery (%) | Single               | 16 (42.11%)      | 21 (51.22%)   | 0.656  |
|                                  | Two                  | 22 (57.89%)      | 20 (48.78%)   | 0.417  |
| Per capita drug-eluting stent     | 2.61 ± 1.15          | 2.27 ± 0.87      | 1.489         | 0.141  |
| Average length of stent (mm)      | 20.65 ± 4.53         | 18.93 ± 5.18     | 1.206         | 0.231  |
| Average diameter of stent (mm)    | 3.06 ± 0.42          | 2.92 ± 0.59      |               |        |

Note: PTA, percutaneous transluminal angioplasty.

3.2. Total Response Rates in the Intervention Group Were Higher Than that in the Control Group

Skin temperature, TcPO₂, ABI, restenosis incidence and ulcer improvement and cure rates in the control and intervention groups are shown in Table 3. Before treatment, in the intervention group, the total score was 14.03 ± 6.10, of which 20 cases (52.63%) were < 15 points, and 15–28 points (excluding 28 points) were 18 cases (47.37%). In the control group, the total score was 13.51 ± 6.13 points, of which 21 cases were < 15 points (51.22%), 19 cases were 15–28 points (excluding 28 points) (46.34%). There was no significant difference in the proportion distribution of total scores before treatment between the two groups (\( p > 0.05 \)), suggesting of comparability. Compared with that before surgery, the scores of the two groups increased notably after treatment (both \( p < 0.05 \)), but there was no significant difference in the distribution of scores between the two groups after treatment (\( p > 0.05 \)). The average scores of the two groups were compared after treatment. The intervention group scores were much higher than that of control group (\( p < 0.05 \)). It can be considered that the intervention group had better results than the control group in terms of signs, clinical symptoms and improvement of foot ulcer.

**Table 3.** Clinical symptoms, signs and foot ulcer conditions of patients before and after treatment in the case and control groups.

| Scores   | Intervention | Control | \( \chi^2/t \) | \( P \) |
|----------|--------------|---------|---------------|--------|
| < 15     | Before treatment | 20      | 21            | 0.0158 | 0.9001 |
|          | After treatment | 5*      | 10*           | 1.779  | 0.1822 |
| 15–28    | Before treatment | 18      | 19            | 0.0084 | 0.9272 |
|          | After treatment | 13      | 17            | 0.5803 | 0.4462 |
| ≥ 28     | Before treatment | 0       | 1             | 0.9387 | 0.3326 |
|          | After treatment | 19*     | 13*           | 2.846  | 0.0916 |
| Average  | Before treatment | 14.03 ± 6.10 | 13.51 ± 6.13 | 0.3776 | 0.7068 |
|          | After treatment  | 26.73 ± 8.64* | 22.53 ± 8.57* | 2.012  | 0.0483 |

Note: Before treatment, n = 38 in the intervention group and n = 41 in the control group. 3 d after treatment, n = 37 in the
intervention group, n = 40 in the control group; 6 months after treatment, n = 34 in intervention group, n = 36 in the control group, p < 0.05 vs. that before treatment.

The total response rates in the control and intervention groups are shown in Table 4. Compared with the control group, effective rate in the intervention group increased significantly, invalid rate in the intervention group decreased significantly (p < 0.05), and valid and aggravating rates had no significant difference (p > 0.05).

Table 4. Total response rate of LEAD patients in the case and control groups.

| Indicators       | Intervention (n = 38) | Control (n = 41) | $\chi^2$ | P     |
|------------------|----------------------|-----------------|---------|-------|
| Effective (%)    | 25 (65.79)           | 14 (34.15)      | 14.34   | 0.0025|
| Valid (%)        | 7 (18.42)            | 8 (19.51)       |         |       |
| Invalid (%)      | 1 (2.63)             | 14 (34.15)      |         |       |
| Aggravating (%)  | 5 (13.16)            | 5 (12.20)       |         |       |
| Total response rate (%) | 32 (84.21) | 22 (53.66)      | 8.51    | 0.0035|

Note: LEAD, lower extremity arterial disease.

3.3. Restenosis Incidence 6 Months and 12 Months after Treatment in the Control and Intervention Groups

Comparison of restenosis incidence between the two groups is shown in Table 5. Six months after treatment, levels of TcPO2, ABI and ulcer healing rate in the intervention group were obviously higher than those in the control group (all p < 0.05), but there were no significant differences in skin temperature, recurrence rate and ulcer improvement rate between the two groups (p > 0.05). Twelve months after treatment, the skin temperature, TcPO2 and ABI levels of the intervention group were much higher than those of the control group (all p < 0.05), while the recurrence rate was notably lower than that of the control group (p < 0.05), and the ulcer improvement rate was dramatically higher. The healing rate of ulcer and ulcer both increased, but there was no significant difference compared with the control group (p > 0.05).

Table 5. Skin temperature, TcPO2, ABI, recurrence rate, ulcer improvement rate, ulcer cure rate in the case and control groups six and twelve months after treatment.

| Indicators       | Intervention (n = 38) | Control (n = 41) | $\chi^2/t$ | P     |
|------------------|----------------------|-----------------|-----------|-------|
| Skin temperature (°C) |                    |                 |           |       |
| Six months after treatment | 32.4 ± 3.9         | 31.8 ± 3.3      | 0.4887    | 0.6962|
| Twelve months after treatment | 32.3 ± 3.7        | 29.2 ± 3.3      | 3.651     | 0.0005|
| TcPO2 (mmHg) |                      |                 |           |       |
| Six months after treatment | 35.5 ± 3.5        | 29.9 ± 3.3      | 6.89      | < 0.001|
| Twelve months after treatment | 34.2 ± 2.9       | 27.9 ± 3.5      | 8.056     | < 0.001|
| ABI |                      |                 |           |       |
| Six months after treatment | 0.89 ± 0.06      | 0.68 ± 0.05     | 15.94     | < 0.001|
| Twelve months after treatment | 0.82 ± 0.04     | 0.54 ± 0.07     | 20.09     | < 0.001|
| Recurrence rate (%) |                      |                 |           |       |
| Six months after treatment | 1 (2.6)          | 2 (4.9)         | 0.9436    | 0.3313|
| Twelve months after treatment | 2 (5.3)         | 11 (26.8)       | 7.069     | 0.0078|
| Ulcer improvement rate (%) |                      |                 |           |       |
| Six months after treatment | 23 (60.5)       | 18 (43.9)       | 2.244     | 0.1341|
| Twelve months after treatment | 27 (71.1)       | 25 (61.0)       | 1.019     | 0.3128|
| Ulcer cure rate (%) |                      |                 |           |       |
| Six months after treatment | 22 (57.9)       | 12 (29.3)       | 6.89      | 0.0087|
| Twelve months after treatment | 23 (60.5)       | 22 (53.7)       | 0.355     | 0.5513|
Note: TcPO$_2$, percutaneous oxygen partial pressure; ABI, ankle brachial index. Intervention group n = 34 and control group n = 36 at 6 months. Intervention group n = 33 and control group n = 35 at 12 months.

3.4. Levels of IL-6, TNF-α and CRP in the case and Control Groups before and after Treatment

Levels of IL-6, TNF-α and CRP in the two groups before and after treatment are showed in Table 6. There was no significant difference for the levels of IL-6, TNF-α and CRP in the intervention and control groups before treatment (all $p > 0.05$). The levels of IL-6, TNF-α and CRP 3 d after treatment increased in both groups ($p < 0.05$), and decreased in the intervention and control groups 6 months after treatment with no significant difference when compared with that before treatment ($p > 0.05$). The levels of IL-6, TNF-α and CRP 3 d and 6 months after treatment was lower in the intervention group than that in the control group (all $p < 0.05$).

Table 6. Levels of IL-6, TNF-α and CRP in the case and control groups before and after treatment.

| Inflammatory factors | Intervention (n = 38) | Control (n = 41) | t    | P    |
|----------------------|-----------------------|-----------------|------|------|
| IL-6 (pg/mL)         |                       |                 |      |      |
| Before treatment     | 8.56 ± 0.98           | 9.27 ± 0.96     | 1.921| 0.159|
| Three days after     | 11.69 ± 1.80$^*$      | 12.88 ± 2.05$^*$| 3.178| 0.0051|
| Six months after     | 8.73 ± 1.38           | 9.69 ± 2.25     | 2.445| 0.0451|
| TNF-α (ng/mL)        |                       |                 |      |      |
| Before treatment     | 1.56 ± 0.54           | 1.69 ± 0.62     | 0.7274| 0.8492|
| Three days after     | 2.58 ± 0.88$^*$       | 3.36 ± 1.27$^*$ | 4.309| < 0.001|
| Six months after     | 1.55 ± 0.30           | 2.02 ± 0.73     | 2.476| 0.0415|
| CRP (mg/L)           |                       |                 |      |      |
| Before treatment     | 3.76 ± 0.43           | 4.19 ± 1.35     | 1.298| 0.4797|
| Three days after     | 6.85 ± 1.95$^*$       | 8.45 ± 2.04$^*$ | 4.768| < 0.001|
| Six months after     | 3.90 ± 0.75           | 4.78 ± 1.50     | 2.501| 0.0388|

Note: *, $p < 0.05$ vs. before treatment; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein. Before treatment n = 38 in case group and n = 41 in control group; 3 days after treatment n = 37 in case group and n = 40 in control group; 6 months after treatment n = 34 in case group and n = 36 in control group.

3.5. Comparison of Adverse Reaction

During the postoperative follow-up period, a total of 11 patients died, and 2 died during the perioperative period, mainly due to postoperative heart failure, multiple organ failure and infection. The main complication rate was 7.59%. Among them, 3 cases had osteofascial compartment syndrome, which improved obviously when discharged from conservative treatment such as incision and reduction. Two cases had postoperative ulcers and toe gangrene. There was no obvious ulcer exacerbation and continued to develop after the operation, who was discharged after treatment. One patient developed a severe pulmonary infection and was discharged after active anti-infective treatment. The total postoperative follow-up rate was 100% in the intervention group and 100% in the control group.

The comparison of the incidence of restenosis between the two groups was as presented in Figure 1. Six months after treatment, the incidence of restenosis in the intervention group was 2.94%, and that in the control group was 19.44%. Comparing the two groups, the incidence of restenosis in the intervention group was lower than that in the control group ($p < 0.05$). Twelve months after treatment, the incidence of restenosis in the two groups both increased. The incidence of restenosis in the intervention group was 18.18%, and the control group was 45.71%. Compared with the control group, the incidence of restenosis in the intervention group reduced sharply ($p < 0.05$). The incidence of restenosis increased remarkably in both groups 12 months and 6 months after treatment ($p < 0.05$).
3.6. Logistic Regression Analysis

The correlation of treatment regimen and baseline characteristics with total recurrence rate of restenosis after intervention was analyzed by logistic regression analysis (forward method), and the results are displayed in Table 7. Restenosis after intervention was the dependent variable, and treatment regimen, baseline characteristics, blood biochemical indicators, angiographic baseline data and PTA results were independent variables. It was suggested that the total recurrence rate of restenosis after intervention shared association with treatment regimen, Fontaine staging, and HbA1c (p < 0.05). PTA treatment alone, Fontaine staging in stage IV, and high glycated hemoglobin are risk factors for restenosis.

Table 7. Risk factors that influenced the total recurrence rate of restenosis after intervention are analyzed by logistic regression analysis

| Factors          | B      | SE  | Wals | Sig   | Exp (B) | 95% CI       |
|------------------|--------|-----|------|-------|---------|--------------|
| Treatment regimen| 1.157  | 0.651| 3.161| 0.075 | 3.181   | 0.888 - 11.395|
| Fontaine stages  | 1.241  | 0.533| 5.418| 0.02  | 3.458   | 1.217 - 9.830 |
| HbA1c            | 0.923  | 0.301| 9.427| 0.002 | 2.517   | 1.396 - 4.536 |
| Constant         | -12.82 | 3.293| 15.153| 0     | 0       | -            |

Note: LEAD, lower extremity arterial disease; HbA1c; glycated haemoglobin A1c.

3.7. Survival Rate Analysis

As presented in Figure 2, 6-month survival rate $X^2 = 0.054$, $p > 0.05$; 12-month survival rate $X^2 = 0.036$, $p > 0.05$; 24-month survival rate $X^2 = 0.009$, $p > 0.05$; 36-month survival rate $X^2 = 0.3151$, $p > 0.05$.

Figure 2. Comparison of survival rate between the two groups after operation.
4. Discussion

The growing aging population serves as a pressing challenge for the increasing number of patients with LEAD [23]. Major surgery and separate interventions are not acceptable for LEAD patients regarding related morbidity by alternative hybrid endovascular dilatation and lower extremity arterial reconstruction [24]. Balloon post-dilation has been proposed as an option to improve safety and effectiveness by obtaining a better expansion of the stent [25,26]. Therefore, we combined DES implantation with PTA to treat patients with LEAD to see how they affect the restenosis and inflammatory reaction for patients LEAD.

On the one hand, we found that DES implantation after PTA could improve treatment efficacy and decrease the restenosis incidence. TcPO2 measurement with an electrode serves as a gas sensor to determine the tension of oxygen diffusing from local skin [27]. TcPO2 is an indicator to provide information of disease severity, leg prognosis, amputation levels, responses to treatment and healing rate [28]. ABI is a basic diagnostic tool of PAD and an indicator of its severity [29]. Its estimation with high specificity and sensitivity is also of importance in diagnosis of lower extremity wounds and necessity for prompt revascularization [30]. The higher level of TcPO2 and ABI means the lower severity degree of LEAD [31]. It has been reported that PTA improved TcPO2 and ABI in lowering the amputation rate successfully [32]. Lower limb ulcers accounted for over 90% in arterial disease, venous disease, and neuropathy cause [33]. Foot ulcer, as the IV stage of LEAD, was developed in 2% to 3% of diabetes annually, and was considered as one of the prognostic indicators for advanced diabetes [34]. PTA has also been reported to cause lower rate of infectious complications [35]. There was also study showing that PTA alone brought recovery of over 70% of iliac lesions and selective stenting offers satisfactory assisted primary and secondary long-term patency after iliac angioplasty [36]. There was a study suggesting that DES implantation as an alternative strategy for the prevention of restenosis [37]. Recently, DES implantation has been proved to be effective in the management of femoropopliteal in-stent restenosis with occlusion [38]. Furthermore, simple balloon dilatation may obtain improvement of restenosis lesions after DES on optical coherent tomography images [39]. In patients with critical limb ischemia caused by LEAD who received DES implantation showed better patency rates and less amputation [40].

On the other hand, the levels of IL-6, TNF-α and CRP in the patients who received PTA and DES implantation were lower than that in the control group 3 d and 6 months after treatment. Overexpression of inflammatory indicators is involved in vascular inflammation, genesis of atherosclerosis, plaque instability and rupture [41]. IL-6, which could be produced from fibroblasts, endothelial cells, T cells, is an indicator of inflammation and trauma response and is often used in diagnosing patients with diabetic foot infections [42,43]. TNF-α, one of the proinflammatory cytokines, is able to promote repair and recovery from infectious and toxic agents [44]. CRP is also an important indicator of chronic inflammation strongly associated with age, gender, ethnicity and body mass index related diseases [45]. CRP was one of the indicators in diabetic patients with infected foot ulcers, decrease of which was also an important outcome of a successful PTA [46]. A study showed that the levels of inflammatory factors including IL-6, TNF-α, and CRP were increased in patients with idiopathic venous thrombosis [47]. Petrovay F et al. also found that percutaneous transluminal coronary angioplasty alone contributed to inflammatory responses in which levels of CRP and IL-6 were elevated [48]. Gupta GK et al. found that expression of TNF-α was significantly increased in tissues with arterial injury after balloon angioplasty [49].

5. Conclusion

Above all, we may conclude that DES implantation after PTA may reduce the restenosis incidence and decrease the levels of IL-6, TNF-α, and CRP so as to improve clinical efficacy in treating patients with LEAD. Along with the development of technology, there must be more reformative DES and balloon equipment, so there should be better regimen waiting to be found.

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