Efficacy and Safety of Drug-Coated Balloon Angioplasty for Lower Extremity Arterial Occlusive Disease: A Meta-Analysis Postprint

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Abstract

Objective To evaluate the efficacy and safety of drug-coated balloon (DCB) angioplasty compared with uncoated balloon (UCB) angioplasty for the treatment of lower extremity arterial occlusive disease using Meta-analysis.

Methods A computerized search was conducted in domestic and foreign databases for relevant randomized controlled trials on DCB and UCB angioplasty for lower extremity arterial occlusive disease. After literature screening and quality assessment according to inclusion and exclusion criteria, Meta-analysis was performed using RevMan 5.3 software. The following outcomes were compared between the two groups: restenosis rate at 6 months postoperatively, late lumen loss, target lesion revascularization rate at 1 year postoperatively, patency rate at 1 year postoperatively, mortality rate at 1 year postoperatively, and amputation rate.

Results A total of 11 trials involving 1853 patients with 2150 arterial lesions were included, with 1110 patients (1288 lesions) in the DCB group and 743 patients (862 lesions) in the UCB group. Meta-analysis results showed that compared with the UCB group, DCB angioplasty significantly reduced the restenosis rate at 6 months postoperatively (15.2% vs 39.0%; OR: 0.28; 95%CI: 0.17~0.48; P<0.00001), late lumen loss (-0.05~0.56 vs 0.54~1.7; WMD: -0.57; 95%CI: -0.93~-0.21), and target lesion revascularization rate at 1 year postoperatively (13.0% vs 28.1%; OR: 0.39; 95%CI: 0.23~0.64; P=0.0002), and improved the patency rate at 1 year postoperatively (71.8% vs 52.9%; OR: 2.32; 95%CI: 1.21~4.43; P=0.001). However, there were no statistically significant differences between the two groups in mortality rate (4.8% vs 5.0%; OR: 1.00; 95%CI: 0.62~1.63; P=0.99) or amputation rate (3.4% vs 2.9%; OR: 1.41; 95%CI: 0.74~2.70; P=0.30).

Conclusion Compared with UCB angioplasty for lower extremity arterial occlusive disease, DCB angioplasty is an endovascular therapy with more significant efficacy and no significant difference in safety.

Full Text

Abstract

Objective: To evaluate the efficacy and safety of drug-coated balloon (DCB) angioplasty versus uncoated balloon (UCB) angioplasty in the treatment of lower extremity arterial occlusive disease (LEAOD) using meta-analysis.

Methods: Randomized controlled trials (RCTs) comparing DCB and UCB angioplasty for LEAOD were systematically searched in major databases. After literature screening and quality assessment according to predefined inclusion and exclusion criteria, meta-analysis was performed using RevMan 5.3 software. The primary outcomes compared between groups included restenosis rate at 6 months, late lumen loss, target lesion revascularization (TLR) rate at 1 year, patency rate at 1 year, mortality rate at 1 year, and amputation rate at 1 year.

Results: Eleven trials involving 1,853 patients with 2,150 arterial lesions were included. The DCB group comprised 1,110 patients with 1,288 lesions, while the UCB group included 743 patients with 862 lesions. Meta-analysis demonstrated that DCB angioplasty significantly reduced the 6-month restenosis rate (15.2% vs. 39.0%; OR: 0.28; 95% CI: 0.17–0.48; $P < 0.00001$), late lumen loss (range: -0.05 to 0.56 mm vs. 0.54 to 1.7 mm; WMD: -0.57; 95% CI: -0.93 to -0.21), and 1-year TLR rate (13.0% vs. 28.1%; OR: 0.39; 95% CI: 0.23–0.64; $P = 0.0002$) compared with UCB angioplasty. The 1-year patency rate was significantly higher in the DCB group (71.8% vs. 52.9%; OR: 2.32; 95% CI: 1.21–4.43; $P = 0.001$). However, no significant differences were observed between groups in mortality rate (4.8% vs. 5.0%; OR: 1.00; 95% CI: 0.62–1.63; $P = 0.99$) or amputation rate (3.4% vs. 2.9%; OR: 1.41; 95% CI: 0.74–2.70; $P = 0.30$).

Conclusion: DCB angioplasty represents a more effective endovascular treatment for LEAOD compared with UCB angioplasty, with no significant difference in safety profile.

Key words: percutaneous transluminal angioplasty; lower extremity arterial occlusive disease; drug-coated balloon; uncoated balloon; randomized controlled trial; meta-analysis

Introduction

Percutaneous transluminal angioplasty (PTA) has been increasingly applied in the treatment of lower extremity arterial occlusive disease (LEAOD) and has gradually become the preferred revascularization strategy [1-2]. This technique eliminates vascular stenosis or occlusion through intraluminal balloon or stent

dilation. However, low long-term patency rates have remained a bottleneck limiting the development of this minimally invasive technique, with 50%–60% of patients developing restenosis or re-occlusion within one year after PTA [3-4]. Although drug-eluting stents can effectively reduce restenosis rates and improve short- and long-term patency [5], their application in LEAOD is somewhat limited by the diffuse nature of lower extremity arterial lesions and vascular tortuosity. Moreover, issues such as stent fracture, migration, and in-stent restenosis persist [4]. Balloon angioplasty is relatively simple, leaves no stent in the vessel lumen, and is less restricted by arterial diameter or location, making it applicable to large and small arteries, joint flexion sites, arterial bifurcations, and long-segment stenoses. Some scholars believe balloon angioplasty will become the mainstay of endovascular treatment for LEAOD [6].

To reduce target lesion restenosis after balloon angioplasty, drug-coated balloons (DCBs) were developed. The efficacy and safety of DCB angioplasty have been demonstrated in animal studies and coronary artery disease [7-8]. However, in the field of LEAOD, its efficacy and safety remain controversial. Multiple RCTs comparing DCB angioplasty with other endovascular techniques for LEAOD have yielded conflicting conclusions: most trials support the superiority of DCB angioplasty in terms of efficacy and safety, while others suggest no significant advantage or even inferior safety compared with other techniques [9, 16-17]. Therefore, this meta-analysis was conducted to evaluate the efficacy and safety of DCB versus uncoated balloon (UCB) angioplasty for LEAOD, providing scientific evidence for clinical application.

Methods

1.1 Inclusion and Exclusion Criteria

Inclusion criteria: (1) RCTs comparing DCB angioplasty with UCB angioplasty for LEAOD; (2) intention-to-treat analysis; (3) follow-up duration 6 months; (4) published in Chinese or English.

Exclusion criteria: (1) Studies involving vascular segments other than lower extremity arteries; (2) interventions including additional treatments beyond DCB or UCB angioplasty; (3) duplicate publications, retrospective studies, case reports, or animal experiments; (4) studies with <20 cases or >10% loss to follow-up.

1.2 Search Strategy

We systematically searched the Cochrane Library, PubMed, Embase, Wanfang Database, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and VIP Database from inception to June 2016. Chinese search terms included: lower extremity artery, femoropopliteal artery, infrapopliteal artery, percutaneous transluminal angioplasty, drug-coated balloon, randomized controlled trial, and their synonyms. English search terms

included: lower extremity artery, femoropopliteal artery, infrapopliteal artery, percutaneous transluminal angioplasty, drug-coated balloon, randomized controlled trial, and their synonyms.

1.3 Data Extraction and Quality Assessment

Two reviewers independently screened literature and extracted data according to inclusion and exclusion criteria. Disagreements were resolved through discussion or consultation with an expert. Authors were contacted for additional information when necessary. The following data were extracted: trial characteristics, baseline patient characteristics, 6-month restenosis rate (defined as >50% stenosis on follow-up), late lumen loss (LLL, defined as the difference between preoperative and 6-month postoperative minimum diameter of the stenotic segment on angiography), 1-year TLR rate, 1-year patency rate, 1-year mortality rate, and 1-year amputation rate.

Quality assessment was performed independently by two reviewers using the Cochrane Collaboration' s tool, evaluating: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants; (4) blinding of investigators; (5) incomplete outcome data; and (6) selective outcome reporting.

1.4 Statistical Analysis

Meta-analysis was performed using RevMan 5.3 software from the Cochrane Collaboration. Heterogeneity was assessed using the ^{2} test. When studies were clinically homogeneous and P > 0.1 with $I^2 < 50\%$, indicating no significant heterogeneity, a fixed-effects model was used. When P 0.1 and I^2 50%, indicating significant heterogeneity, sources of heterogeneity were explored through sensitivity analysis, and a random-effects model was applied. Dichotomous data were expressed as odds ratios (OR) with 95% confidence intervals (CI), while continuous variables were expressed as weighted mean differences (WMD) with 95% CI. Publication bias was assessed using funnel plots, with statistical significance set at = 0.05.

Results

2.1 Literature Search and Study Characteristics

The literature screening process identified 11 RCTs [Figure 1: see original paper], of which nine were multicenter designs [10-11, 14-20]. All included trials used paclitaxel-coated balloons with drug concentrations of 2–3.5 g/mm². One trial included an intermediate group (n = 52) that received UCB angioplasty with paclitaxel-dissolved contrast medium, which was excluded from this analysis [20]. The remaining 10 trials randomly assigned patients to DCB or UCB groups. A total of 1,853 patients with 2,150 arterial lesions were included: 1,110 patients (1,288 lesions) in the DCB group and 743 patients (862 lesions) in the UCB group. Baseline patient characteristics are summarized in Table 1 . Two trials

included lesions in the femoral, popliteal, and infrapopliteal arteries [10, 13]; six trials involved femoral and popliteal arteries [14, 16-20]; and three trials included only infrapopliteal arteries [11-12, 15]. Target lesion characteristics are presented in Table 2 .

All patients received antiplatelet therapy, including loading doses of aspirin and clopidogrel before angioplasty, followed by dual antiplatelet maintenance therapy for at least one month. In a small proportion of lesions (~7.0%), bare metal stents were implanted due to residual severe stenosis after balloon angioplasty. The mean follow-up duration was 16.4 months, with all trials including angiographic follow-up data at 6–12 months.

2.2 Quality Assessment

All studies employed randomization, with some reporting allocation concealment. All studies implemented blinding of participants, while blinding of investigators was not feasible due to the distinct appearance of DCB and UCB devices. No studies had incomplete data reporting or selective outcome reporting (Table 3).

2.3 Meta-Analysis Results

2.3.1 Restenosis Rate at 6 Months Five trials reported 6-month restenosis rates. No significant heterogeneity was observed ($I^2 = 0\%$, $P = 0.91$), and a fixed-effects model was used. Meta-analysis showed a statistically significant difference, with DCB group restenosis rates substantially lower than UCB group rates (15.2% vs. 39.0%; OR: 0.28; 95% CI: 0.17–0.48; $P < 0.00001$) [Figure 2: see original paper].

2.3.2 Late Lumen Loss Six trials reported 6-month late lumen loss. Significant heterogeneity was present ($I^2 = 70\%$, $P = 0.005$), requiring a random-effects model. Meta-analysis revealed a statistically significant difference, with DCB group late lumen loss significantly smaller than UCB group loss (range: -0.05 to 0.56 mm vs. 0.54 to 1.7 mm; WMD: -0.57; 95% CI: -0.93 to -0.21; $P = 0.002$) [Figure 3: see original paper].

2.3.3 Target Lesion Revascularization Rate at 1 Year Ten trials reported 1-year TLR rates. Significant heterogeneity was observed ($I^2 = 67\%$, $P = 0.001$), and a random-effects model was applied. Meta-analysis demonstrated a statistically significant difference, with DCB group TLR rates markedly lower than UCB group rates (13.0% vs. 28.1%; OR: 0.39; 95% CI: 0.23–0.64; $P = 0.0002$) [Figure 4: see original paper].

2.3.4 Patency Rate at 1 Year Three trials reported 1-year patency rates. Significant heterogeneity was present ($I^2 = 73\%$, $P = 0.02$), necessitating a random-effects model. Meta-analysis showed a statistically significant difference,

with DCB group patency rates higher than UCB group rates (71.8% vs. 52.9%; OR: 2.32; 95% CI: 1.21–4.43; P = 0.01) [Figure 5: see original paper].

2.3.5 Mortality Rate at 1 Year Nine trials reported 1-year mortality rates. No significant heterogeneity was observed ($I^2 = 0\%$, P = 0.63), and a fixed-effects model was used. Meta-analysis revealed no statistically significant difference between DCB and UCB groups (4.8% vs. 5.0%; OR: 1.00; 95% CI: 0.62–1.63; P = 0.99) [Figure 6: see original paper].

2.3.6 Amputation Rate at 1 Year Eight trials reported 1-year amputation rates. No significant heterogeneity was present ($I^2 = 0\%$, P = 0.66), and a fixed-effects model was applied. Meta-analysis showed no statistically significant difference between DCB and UCB groups (3.4% vs. 2.9%; OR: 1.41; 95% CI: 0.74–2.70; P = 0.30) [Figure 7: see original paper].

2.4 Sensitivity Analysis

Among the six meta-analyses, three results (late lumen loss, 1-year TLR rate, and patency rate) exhibited heterogeneity, but consistent results were obtained using both random-effects and fixed-effects models. For late lumen loss, the BIOLUX P-II trial [11] contributed substantial heterogeneity; after its removal, heterogeneity decreased ($I^2 = 12\%$, P = 0.43) without changing the meta-analysis result (WMD: -0.69; 95% CI: -0.93 to -0.46; $P < 0.00001$). For 1-year TLR rate, no single study contributed markedly to heterogeneity. For 1-year patency rate, the IN.PACT SFA trial [16] contributed substantial heterogeneity; after its exclusion, heterogeneity resolved ($I^2 = 0\%$, P = 0.97) without altering the result (OR: 1.68; 95% CI: 1.15–2.45; P = 0.007). Heterogeneity may be attributed to variations in operator experience across centers and differences in methodological quality, suggesting both clinical and statistical heterogeneity; however, results remained consistent across different models and after excluding outlier studies.

2.5 Publication Bias

Funnel plot analysis of the primary outcome (1-year mortality) showed that the nine included RCTs were symmetrically distributed around the effect line within the 95% confidence limits, indicating minimal publication bias [Figure 8: see original paper].

Discussion

Post-PTA restenosis primarily results from intimal hyperplasia and atherosclerosis, representing an excessive vascular response to mechanical injury. Endovascular manipulation causes varying degrees of vascular wall injury, with exposed collagen fibers promoting platelet deposition and thrombus formation. Inflammatory cell aggregation (neutrophils, macrophages, and T cells) at the

injury site triggers inflammatory responses that activate oncogenes in vascular smooth muscle cells, leading to proliferation and eventual luminal narrowing [21]. DCBs deliver antiproliferative and anti-inflammatory drugs (such as paclitaxel and sirolimus) directly to the lesion through balloon expansion, with 75% of the drug rapidly penetrating the arterial wall to inhibit smooth muscle cell migration and proliferation, thereby preventing PTA restenosis [22]. Theoretically, DCBs can improve target vessel patency while avoiding potential risks associated with stent implantation.

This meta-analysis of 11 RCTs (1,853 patients with 2,150 lesions) demonstrated that DCB angioplasty significantly reduced 6-month restenosis rates and late lumen loss, decreased the need for repeat revascularization, and improved patency rates compared with UCB angioplasty, with no significant differences in mortality or amputation rates. These findings suggest that DCB angioplasty effectively inhibits smooth muscle cell proliferation and prevents restenosis, thereby improving vessel patency. We recommend prioritizing DCB angioplasty in endovascular treatment of LEAOD, particularly for complex lesions involving infrapopliteal, bifurcation, and distal arteries, given its high success rate, broad applicability, absence of residual stents, and unrestricted options for future retreatment.

Several limitations may affect the strength of these conclusions. First, only four of the 11 included RCTs implemented allocation concealment [10, 12, 14, 20], and blinding of investigators was impossible due to the distinct appearance of DCB and UCB devices. Second, there was no uniform antiplatelet regimen or standardized criteria for TLR across trials. Third, the mean follow-up duration of 16.4 months is relatively short, requiring longer-term data to evaluate the durability of DCB angioplasty. Fourth, the included trials used different balloon devices, and with continuous innovation in interventional technology and the emergence of new drug-coated devices, further clinical trials are warranted.

In summary, DCB angioplasty is a more effective endovascular treatment for LEAOD compared with UCB angioplasty, with comparable safety. However, as endovascular technology continues to evolve, additional comparative studies of DCBs are needed to guide clinical practice.

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Note: Figure translations are in progress. See original paper for figures.