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Review

Paclitaxel-coated versus uncoated balloon angioplasty for femoropopliteal artery in-stent restenosis

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HIGHLIGHTS

- A comprehensive literature review and quantitative analysis were conducted.
- DCBA is associated with superior efficacy outcomes compared with POBA with the same safety outcome after a one-year follow-up.
- DCBA is a reliable and promising strategy in the treatment of femoropopliteal artery ISR.

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ABSTRACT

Background: Several prospective controlled trials have assessed the safety and efficacy of drug-coated balloon angioplasty (DCBA) versus standard balloon angioplasty (POBA) for femoropopliteal in-stent restenosis (ISR). We therefore performed a meta-analysis of prospective controlled trials to pool the results of these trials and obtain more reliable conclusions.

Methods and results: Prospective controlled trials comparing DCBA versus POBA were searched through PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, ISI Web of Knowledge, and relevant websites without language or publication date restrictions. The keywords were "drug-eluting balloon," "angioplasty," "femoropopliteal," and "in-stent restenosis." We selected recurrent ISR, freedom from clinically driven target lesion revascularization (TLR), clinical improvement, ankle-brachial index (ABI), and major adverse events (MAEs) as the outcomes of this meta-analysis. Based on the inclusion criteria, we identified 3 prospective clinical trials. The one-year outcomes of DCBA and POBA were as follows: recurrent ISR (34.8% versus 73.1%, respectively; OR, 0.18; 95% CI, 0.10–0.32, $Z = 5.56$, $P < 0.00001$), freedom from clinically driven TLR (82.2% versus 54.1%, respectively; OR, 4.20; 95% CI, 2.05–8.61, $Z = 3.92$, $P < 0.0001$), clinical improvement (76.2% versus 55.7%, respectively; OR, 2.58; 95% CI, 1.41–4.72, $Z = 3.07$, $P = 0.002$), ABI (MD, −0.04; 95% CI, −0.13–0.04, $Z = 1.01$, $P = 0.31$), and MAEs (11.0% versus 18.3%, respectively; OR, 0.54; 95% CI, 0.25–1.15, $Z = 1.60$, $P = 0.002$).

Conclusions: For femoropopliteal ISR, DCBA is associated with superior efficacy outcomes compared with POBA, with the same safety outcome after a one-year follow-up. In the future, multicenter and large-scale prospective controlled trials comparing DCBA with other endovascular strategies are required to further assess the efficacy and safety profiles of DCBA in the treatment of femoropopliteal ISR.

1. Introduction

Endovascular therapy has become the primary method of treating chronic peripheral arterial disease (PAD) [1]. Compared with percutaneous transluminal angioplasty (PTA), stenting is more frequently used in femoropopliteal arterial occlusive disease, especially for advanced situations such as long segmental lesions [2]. However, the treatment outcomes have not reached initial expectations. The main challenges are the risks of fracture,

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restenosis, thrombosis, and the inflammatory and proliferative responses of the arterial wall [3,4]. With notable improvements in stenting devices and techniques in recent years, procedural complications such as stent fracture have been dramatically reduced. However, in-stent restenosis (ISR) remains a common and frustrating problem for endovascular specialists [5]. Indeed, the 12-month rates of ISR after implantation of nitinol stents in the femoropopliteal artery range from 18% to 37%, and its incidence is higher for longer lesions (>15 cm) [6].

Currently, several treatment methods are used for ISR, including PTA with or without a drug-coated balloon, repeat stenting, cutting balloon angioplasty, cryoplasty, and laser or directional atherectomy [7]. Among them, standard balloon angioplasty (POBA) is the initial strategy. Many prospective trials have assessed the clinical usefulness of these methods in the treatment of femoropopliteal ISR. Most trials have compared one type of treatment strategy with POBA, and showed promising results. However, fewer trials have made a horizontal comparison between these methods. Therefore, the optimal strategy for the treatment of femoropopliteal ISR remains unknown. The endovascular treatment of this condition remains a challenge for physicians. Drug-coated balloon angioplasty (DCBA) has been proven useful for the treatment of femoropopliteal occlusive disease and coronary ISR and is promising for femoropopliteal ISR disease [8]. Recently, three prospective clinical trials have assessed the safety and efficacy of DCBA versus POBA for femoropopliteal ISR. The results are not totally consistent and still have some controversy.

From this background, we performed a meta-analysis to assess the overall outcomes from all prospective controlled trials to compare the results of DCBA versus POBA for femoropopliteal ISR. The purpose of this study was to pool similar trials to obtain more reliable results.

2. Methods

2.1. Eligibility criteria

We established a pre-specified protocol for this meta-analysis. Eligible trials fulfilled the following criteria: (1) prospective controlled trial; (2) compared DCBA and POBA in femoropopliteal artery in-stent restenosis; (3) a minimum follow-up of 6 months; (4) intension-to-treat analysis; and (4) reported at least one of the following outcomes - recurrent ISR, freedom from clinically driven target lesion revascularization (TLR), clinical improvement, ankle-brachial index (ABI), major adverse events (MAEs). We excluded reviews and studies that did not provide data to calculate summary statistics. Studies with incomplete data for demographic or clinical variables were still included.

2.2. Information sources and search strategy

We performed a systematic search of the literature according to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. The search was applied to PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, ISI Web of Knowledge, and other relevant websites without language or publication date restrictions. Experts in this field were consulted, and professional inquiries were obtained. The medical subject headings and keywords used to identify relevant articles were “drug-eluting balloon,” “angioplasty,” “femoropopliteal,” and “in-stent restenosis.” The most recent search was performed in July 2016.

2.3. Study selection and assessment of risk of bias

One author screened the studies by title and abstract for inclusion. The identified articles were assessed independently by another author to confirm their eligibility. Those studies that qualified for a full-text review were reviewed by 2 independent reviewers for inclusion in the analysis. The risk of bias was evaluated in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [10] based on the following methodological items: sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. Any disagreements between the reviewers were arbitrated by discussion with the entire group.

2.4. Efficacy and safety outcome variables

Based on the Society for Vascular Surgery/American Association for Vascular Surgery reporting standards for endovascular procedures [11], we chose recurrent ISR, freedom from clinically driven TLR, clinical improvement, and ABI as the efficacy outcomes and MAEs as the safety outcome of this meta-analysis.

Recurrent ISR was defined as a >50% diameter stenosis by angiography or a peak systolic velocity ratio $\geq$2.5 within the treated arterial segment. Clinical improvement was defined as a $\geq$1 Rutherford category improvement after treatment. MAEs included all-cause death, myocardial infarction, major amputation, major bleeding, and thrombosis or surgical intervention related to the target limb.

2.5. Data extraction

A database sheet was developed, tested in 1 randomly selected study, and then refined accordingly. We attempted to collect all possible relevant information. One author extracted the data from the included studies, and another author double-checked the extracted data. The abstracted data included the following: (1) clinical and demographic characteristics (age, male gender, diabetes mellitus, coronary artery disease, chronic kidney disease, smoking, hypertension, dyslipidemia, ABI, lesion length, Rutherford class, ISR Tosaka classification, inclusion criteria, exclusion criteria, post-procedure antiplatelet therapy, and angiographic follow-up) and (2) primary and secondary outcomes (recurrent ISR, freedom from TLR, clinical improvement, ABI, and MAEs). Incomplete data were not pursued by the study authors.

2.6. Statistical analysis

The statistical analyses were performed on an intention-to-treat basis using RevMan software (Version 5.2, The Cochrane Collaboration) and Stata 11 statistical software (STATA Corp, College Station, TX). The odds ratio (OR) with 95% confidence interval (CI) and weighted mean difference (WMD) were used as the summary statistics. Heterogeneity between studies was examined by the chi-square (X^2) test and inconsistency (I^2) statistic. P values < 0.1 indicated significant heterogeneity. I^2 values < 25% indicated low heterogeneity, 25%–50% indicated moderate heterogeneity, and >50% indicated high heterogeneity. The pooled ORs and WMDs were calculated by the Mantel-Haenszel (M-H) fixed-effect model for categorical and continuous variables, respectively. If significant heterogeneity existed, the random-effects model was used. Publication bias was assessed by funnel plot, Egger's test, and Begg's test. Finally, a sensitivity analysis was conducted to determine the potential influence of each study on the overall meta-analysis estimates. This analysis was conducted