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Review

Drug-eluting stents versus control therapy in the infrapopliteal disease: A meta-analysis of eight randomized controlled trials and two cohort studies

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HIGHLIGHTS

- The results of the present meta-analysis indicate the non-superiority of infrapopliteal DES therapy over control therapies (BMS and PTA) with respect to long-term benefits.
- Further randomized trials focusing on clinical endpoints and with longer follow-up are required for endovascular treatment for patients with occlusive disease of infrapopliteal arteries.

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ABSTRACT

Backgroud: Drug-eluting stents (DES) have been proposed for the treatment of infrapopliteal arteries disease. However, the long-term clinical impact of DES treatment in the vascular territory still remains uncertain.

Methods and results: Pubmed, Embase, Cochrane data, CNKI and Wanfang Data were searched until December 20, 2016 for eligible studies according to identical strategies. Additional data were manually retrieved. STATA ver. 12.0 software were used to Meta-analyze the efficacies of DES and control treatment (BMS or PTA) for infrapopliteal arteries disease.

A total of 927 patients from 10 studies (8 randomized controlled trials and 2 cohort studies) were assigned to DESs (n = 484) versus control treatment (n = 443). The results showed that infrapopliteal DES therapy yielded higher primary patency and EFS, while decreased the risk of restenosis at 12-months compared to controls significantly. At 3 years there were no significant differences between two groups, pooled RRs and 95% CI were 1.639 [0.526–5.105], P = 0.394; 1.197 [0.432–3.317], P = 0.729 and 0.992 [0.960–1.024], P = 0.661, respectively. Subgroup analysis showed that infrapopliteal DES therapy using Sirolimus-eluting stents rather than Everolimus-eluting stents provided higher clinic benefits. Infrapopliteal DES therapy yielded no significant difference for TLR, overall survival, Rutherford-Becker class improvement, limb amputation at 12-months and 3-years compared with control treatment.

Conclusions: The results of the present meta-analysis indicate the non-superiority of infrapopliteal DES therapy over control therapies (BMS/PTA) at 3 years, although short-term benefits at 12 months after DES therapy were evident. Further randomized trials with longer follow-up are required to provide the best scientific evidence regarding the preferred endovascular treatment for patients with occlusive disease of infrapopliteal arteries.

Infrapopliteal arterial and below-the-knee (BTK) arterial occlusive disease are the primary causes of critical limb ischemia (CLI) [1,2]. Although clinic progress have obtained recent years, the prognosis for patients with CLI is poor, 30% of patients will have major amputation and 25% may have died in one year [3]. Percutaneous plain balloon angioplasty (PTA) and bare metal stenting

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(BMS) are minimally invasive endovascular techniques that are well established as first-line treatments for infrapopliteal arterial disease in place of traditional femorodistal BTK bypass surgery [4–6]. Although these methods had satisfactory technical success and limb salvage rates compared to bypass surgery, vascular restenosis and the requirement for repeated procedures have emerged as major drawbacks in short-term follow-up [7]. Recently, drug-eluting stents (DES) have been introduced as a viable solution to reduce the incidence of restenosis of BTK arteries and produce more clinical benefits than PTA or BMS [8]. Several meta-analyses and reviews indicated that DES for focal BTK lesions significantly inhibit vascular restenosis, thereby improving primary patency, prolonging overall event-free survival (EFS), decreasing repeat procedure rate, and providing clinical evidence regarding the preferred endovascular treatment of patients with occlusive disease of infrapopliteal arteries [9–11]. However, most of these studies focused on short-term clinical improvement (12 months in most studies). Furthermore, the superiority of DES in its clinical advantages, such as Rutherford category class (RC) improvement, major amputation, and mortality benefits, are still controversial [12]. At last but not at the least, related data from Asian countries were not used in these published meta-analyses. Therefore, this meta-analysis, in which available randomized clinical trials (RCT) and non-randomized cohort trials (NCT) were included was performed to assess the long-term overall outcomes of clinic trials, comparing the results of DES versus control therapy (BMS or PTA) for infrapopliteal arterial disease worldwide and thus may providing updated recommendations for clinical use.

1. Materials and methods

1.1. Study selection

The study protocol, including the formulation of the objectives of the analysis, inclusion/exclusion criteria, and assessments of quality, primary outcomes, and statistical methods, was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [13]. We performed a systematic search in PubMed, Ovid Embase, the Cochrane library, the China National Knowledge Infrastructure database (China), and Wanfang Data (China) for relevant articles published up to December 20, 2016, using the following search terms: “drug-eluting stent,” “angioplasty,” “bare metal stent,” “infrapopliteal,” “below the knee,” “peripheral arterial disease,” “critical limb ischemia,” and “trial,” as well as relevant terms and the corresponding medical subject headings [10]. We filtered all eligible articles and searched the reference lists for additional useful reports. The literature search was performed independently by two reviewers. Any disagreement was resolved by consensus with a third reviewer. The authors of eligible studies were contacted if it was thought that they might have additional useful data.

1.2. Inclusion and exclusion criteria

The inclusion criteria for the primary studies were as follows: trials including patients with infrapopliteal arterial stenosis disease or CLI; interventions that compared DES with control therapy (BMS or PTA); the availability of data regarding clinical outcomes, such as primary patency, binary restenosis, target lesion revascularization (TLR), Event-free survival (EFS), and change in Rutherford classification, as well as wound healing, amputation, death from all causes for follow-up periods of at least 6 months; and publication in English or Chinese. Exclusion criteria for primary studies were as follows: overlap between trials or use of duplicate data, cellular or animal studies, examination of other vascular disease(s), insufficient data for demographic or clinical variables could be extracted, and inclusion of less than 10 patients or case reports.

1.3. Data extraction and literature quality assessment

Two investigators independently extracted data. Discrepancies were resolved by a third reviewer. The following information was extracted from the main text, survival curves, and tables of the articles: first author and publication date; type of study, study period, sample size, age, sex, and follow-up treatment; treatment arms; and primary outcome. The Jadad scale was applied to assess the quality of randomized controlled trials and the Newcastle–Ottawa Scale was applied to assess the quality of NCT. Two reviewers assessed the quality of the included studies, and a third reviewer was consulted in the case of differences in their assessments.

1.4. Statistical analysis

Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for binary variables, including primary patency, restenosis occurrence, TLR, EFS, patient survival, limb amputation, wound healing, and RC improvement at different follow-up times (6 months, 12 months, and 3 years). Heterogeneity among studies was assessed using Cochran's Q test and Higgins's I^2. For $I^2 < 50\%$, the given study was considered to exhibit acceptable heterogeneity and a fixed effects model was used; otherwise, a random effects model was employed. Publication bias was evaluated by constructing a funnel plot using Egger's and Begg's tests. $P < 0.05$ was considered to indicate a statistically significant publication bias. In addition, “trim and fill” analyses were used to evaluate the reliabilities of meta-analytic data if the plots were asymmetric. All analyses were performed using STATA software (ver. 12.0; Stata Corp., College Station, TX, USA).

2. Results

2.1. Search results

After reviewing the titles and abstracts, 10 articles detailing eight randomized controlled trials and two cohort trials were included in the study. A flow diagram of the selection procedure is shown in Fig. 1.

2.2. Baseline characteristics

As shown in Table 1, 927 patients were described in 10 articles (6 from Germany [14–19], 2 from Greece [20,21], 1 from Poland [22], and 1 from China [23]) published between 2002 and 2015. Of the 10 studies, the numbers of cases ranged from 36 to 200 (median, 74.5). The overall proportion of males was 69.04%. Clinically, 90% of studies (9/10) described positive results. All studies had Jadad/NOS scores of 4–5/8–9, indicating that they were of good quality (Table 1). The severity of the disease was almost the same in all articles included in the analysis, and the main inclusion criterion was Rutherford Class 3–6. Primary patency, binary restenosis, TLR, EFS, and other outcomes were investigated in almost all studies. Primary patency was defined as maintained as long as angiographic visualization detected flow within the previously treated lesion without any additional repeat interventional procedure. Binary restenosis was defined as > 50% narrowing of the lumen within the implanted stent. TLR was defined as repeat percutaneous intervention or surgical bypass graft resulting from angiographic evidence of restenosis. EFS was defined as a composite endpoint including freedom from death, major or minor amputation, and any