Meta-Analysis on Clinical Outcomes of Paclitaxel-Coated Balloon Angioplasty in Femoral Popliteal Artery Occlusion

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We attempt to systematically evaluate the clinical effects of different doses of paclitaxel-coated balloon angioplasty in the treatment of femoral popliteal artery occlusion. Using a networked computer, conducting keywords researches including paclitaxel-coated balloon angioplasty and randomized controlled trial for femoral popliteal artery occlusions by the Chinese National Knowledge Infrastructure, Wan Fang Data, China Biology Medicine disc, PubMed and the Cochrane Library, and the search period was up to 31 December 2022. The literature was screened according to inclusion and exclusion criteria, and data from the literature were extracted for meta-analysis to investigate the clinical effects of different doses of paclitaxel-coated balloon. This study included 9 research papers involving 1461 patients, and the baseline information was comparable between all patient groups (p>0.05). The standard dose as well as the low-dose paclitaxel-coated balloon had a smaller rate of (late lumen loss), >50 % restenosis, and target lesion revascularization than the uncoated balloon at 6 mo postoperatively. The rate of >50 % restenosis and target lesion revascularization after standard-dose paclitaxel-coated balloon was smaller than that of low-dose paclitaxel-coated balloon (p<0.05). No statistical difference was found between standard-dose paclitaxel-coated balloon and low-dose paclitaxel-coated balloon in terms of late lumen loss, amputation rate and mortality at 6 mo postoperatively (p>0.05). For the treatment of patients with femoral popliteal artery occlusions, treatment with paclitaxel-coated balloon is superior to uncoated balloon. Compared with low-dose paclitaxel-coated balloon, the use of standard-dose paclitaxel-coated balloon further reduces the postoperative restenosis rate by 50 % and reduces target lesion revascularization, and standard-dose paclitaxel-coated balloon has better clinical results.

Key words: Paclitaxel, balloon angioplasty, femoral popliteal artery occlusions, meta-analysis

Femoropopliteal artery lesions are lesions of the femoral and popliteal arteries, which can have a serious impact on the blood supply to the lower extremities due to its location on the main route of the lower extremity arteries, resulting in ischemia and necrosis of the lower extremities[1]. There are various methods of treating popliteal artery lesions, of which balloon angioplasty is an effective measure. Balloon angioplasty is a modern medical technique that is widely used to treat all types of arterial occlusive conditions[2]. Studies have compared the clinical outcomes of Paclitaxel-Coated Balloon (PCB) angioplasty with those of Uncoated Balloon (UCB)[3], however, the dose of PCB varied between studies[4]. For this reason, this study investigated the clinical effects of different doses of PCB angioplasty in the treatment of femoral popliteal artery occlusions by meta-analysis. This study screened the literature according to the PICOs principles. In inclusion criteria, the literature was studied in patients with superficial femoral or/and popliteal artery stenosis/occlusion; the treatment measures were compared by PCB and UCB, with standard doses of PCB being paclitaxel concentrations of 3.0-3.5 μg/mm^2; low doses of PCB being paclitaxel concentrations of 2.0 μg/mm^2 ; the patients were followed up for at least 6 mo after surgery; the type of study was an Randomized Controlled Trial (RCT); there was no restriction on the language of the literature. In exclusion criteria, the literature was a review, case study analysis or non-clinical study; the length of follow-up was less than 6 mo; the description of the results did not provide data that could be analyzed. Chinese National Knowledge Infrastructure (CNKI), WanFang Data, China Biology Medicine disc (CBM disc), PubMed and the Cochrane Library

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were searched using a networked computer, and the English search terms were femoral artery, popliteal artery, femoropopliteal, infrainguinal, eluting balloon, coated balloon, releasing balloon and plain balloon. The Chinese search terms were "paclitaxel-coated balloon angioplasty", "femoral popliteal artery occlusion". A combination of subject terms and free terms was used, and the search time frame was set from database creation up to 31 December 2022. In this study, two clinically experienced doctors were fixed for literature screening and data extraction. In case of disagreement between the two doctors on the selected literature, a third doctor with senior title and clinical experience was selected at this time to study the content of the literature and to determine whether the literature was included or not, taking into account the opinions of the two previous doctors. The included literature was extracted for information on study design, general information, intervention methods, assessment indicators, adverse events, etc. This study used "the Cochrane handbook for the systematic evaluation of interventions"[5], the risk of bias was assessed using the risk of bias assessment tool in Handbook 5.1.0. The level of risk of bias was assessed by two researchers, and if two researchers did not agree on the risk assessment of the same literature, the third researcher assessed the risk of bias of the literature and processed it according to the opinions of the first two researchers, and finally the literature with "low" risk of bias was included in the study. The quality of evidence was graded using the GRADE system, and the quality of evidence was classified as "high", "moderate", "low" and "very low" in the light of the actual situation, and those with "high" quality evidence were included in the study[6]. In this study, data from the included literature were extracted and analyzed using RevMan 5.3 software as well as state. If $p>0.1$ and $I^2<50$ %, it indicated good homogeneity between studies and was analyzed with a fixed effects model; if $p\leq0.1$ and $I^2>50$ %, it indicated heterogeneity between studies and was analyzed for the source of heterogeneity, and if the results were still heterogeneous, it was analyzed with a random effects model. If there was no heterogeneity in the results, they were analyzed using a fixed-effects model. This study retrieved 196 relevant papers, including 101 papers from CNKI, 47 papers from Wan Fang Data, 31 papers from Qcvip, 13 papers from CBNdisc, 8 papers from Cochrane Library, and 2 papers from other resources; the inclusion and exclusion criteria were used for screening, and 56 duplicate papers were excluded, 24 articles were excluded by reading the titles and abstracts, and 12 articles were excluded by reading the full text, 9 papers were eventually included in the study[6-14]. The included research literature was all domestic clinical medical studies in China, with 1461 patients included, among them, 807 patients in the observation group (or intervention group/ experimental group) and 654 patients in the control group (or conventional group); the largest sample size in the literature was 314 patients and the smallest was 52 patients. The primary indicators were the number of Late Lumen Loss (LLL) in the literature at 6 mo was 5 papers; the first stage patency rate at 1 y was 3 papers and the 1 y<50 % restenosis rate was 1 paper. Secondary indicators included 6-mo and 1 y >50 % restenosis rates, ABI, Rutherford classification, amputation rate, thrombosis rate, and Clinically Driven-Target Lesion Revascularization (CD-TLR) as shown in Table 1. All 9 studies included in this study were RCT studies, all were grouped by randomization and were open studies with no blinding of subjects or investigators, no missing outcome indicators and all baseline data were comparable ($p>0.05$). Among the nine papers included in the study, there are five papers for LLL at 6 mo postoperatively were followed up. After a heterogeneity test, $I^2=47$ %, $p<0.05$, and a random-effects model were used to analyses the results, which showed that LLL at 6 mo postoperatively was less than UCB for both the standard dose as well as the low dose of PCB ($p<0.05$), and no statistically significant differences were seen in the comparison between LLL at 6 mo postoperatively for the standard dose as well as the low dose of PCB ($p>0.05$). Among the nine papers included in the study, there are three followed up the postoperative >50 % restenosis rate, which was tested for heterogeneity, $I^2=49$ %, $p<0.05$, and analyzed using a random effects model, showing that the postoperative >50 % restenosis rate was smaller for standard-dose as well as low-dose PCB than for UCB ($p<0.05$), and that the postoperative >50 % restenosis rate for standard-dose PCB was smaller than for low-dose PCB ($p<0.05$) as shown in Table 2. All nine papers included in the study tracked data on TLR, tested for heterogeneity, $I^2=40$ %, $p>0.05$, and analyzed using a fixed effects model, which showed that the postoperative TLR rate was smaller for standard-dose as well as low-dose PCBs than for UCB ($p<0.05$), and the postoperative TLR rate for standard-dose PCBs was smaller than for

low-dose PCBs ($p<0.05$) as shown in Table 3. Of the nine papers included in the study, six followed up on postoperative amputations and three followed up on postoperative deaths. The I^2 for postoperative amputation and death were tested for heterogeneity at 0; $p>0.05$, and analyzed using a fixed-effects model, which showed that there was no statistical difference in postoperative amputation and mortality rates between standard and low doses of PCB at UCB ($p>0.05$), nor between standard and low doses of PCB ($p>0.05$). Femoral popliteal artery occlusion is a common vascular disease that causes ischemic pain in the lower limbs and pain on exercise. The main cause of this disease is atherosclerosis[15].

TABLE 1: LLL AT 6 MO POSTOPERATIVELY

Author	Paclitaxel dose (μg/mm2)	Experimental group		Reference group		Mean difference (95 % CI)
		Number of occurrences	Total number of samples	Number of occurrences	Total number of samples	
Jia *et al.*[6]	3	20	89	63	89	-1.10 (-1.34, 0.86)
Scheinert *et al.*[7]	3	3	26	9	26	-0.53 (-1.00, 0.06)
Tepe *et al.*[8]	3	20	72	37	89	-0.46 (0.80, 0.12)
Fanelli *et al.*[9]	2	9	53	26	55	-1.14 (1.54, 0.74)
Werk *et al.*[10]	2	6	31	16	34	-0.50 (-1.04, 0.04)

TABLE 2: POSTOPERATIVE RESTENOSIS RATE (>50 %)

Author	Paclitaxel dose (μg/mm²)	Experimental group		Reference group		Hazard level (95 % CI)
		Number of occurrences	Total number of samples	Number of occurrences	Total number of samples	
Jia *et al.*[6]	3	7	89	38	89	0.18 (0.09, 0.39)
Scheinert *et al.*[7]	3	4	26	10	26	0.37 (0.13, 1.02)
Krishnan *et al.*[11]	2	5	191	22	103	0.12 (0.05, 0.30)

TABLE 3: POSTOPERATIVE TLR RATES

Author	Paclitaxel dose (μg/mm²)	Experimental group		Reference group		Mean difference (95 % CI)
		Number of occurrences	Total number of samples	Number of occurrences	Total number of samples	
Jia *et al.*[6]	3	7	89	38	89	0.18 (0.09, 0.39)
Scheinert *et al.*[7]	3	4	26	10	26	0.37 (0.13, 1.02)
Tepe *et al.*[8]	3	13	72	26	89	0.47 (0.26, 0.84)
Fanelli *et al.*[9]	2	9	53	17	55	0.51 (0.24, 1.03)
Werk *et al.*[10]	2	5	31	15	34	0.34 (0.14, 0.92) (-0.28 (0.12, 0.63)
Krishnan *et al.*[11]	2.5	6	191	21	103	0.25 (0.08, 0.86)
Schroeder *et al.*[12]	3	5	207	22	107	0.28 (0.14, 0.65)
Tepe *et al.*[13]	3	3	42	12	43	0.24 (0.22, 0.37)
Liistro *et al.*[14]	2	7	96	28	108	0.29(0.21, 0.57)

Atherosclerosis is the thickening and hardening of the walls of blood vessels, resulting in vascular narrowing or occlusion. The popliteal artery is a very important part of the blood circulation in the lower limbs of the body and is responsible for transporting blood to the knee and lower leg. If the popliteal artery becomes occluded, it can lead to ischemia in the lower limbs, which can lead to pain and other serious complications. There are many different ways to treat popliteal artery occlusion. Some of the more common forms of treatment include medication, interventional therapy and surgery. Medication is usually administered with anti-platelet drugs and vasodilators. Interventional treatment involves the placement of stents or balloon dilation techniques in the narrowed or occluded artery to restore blood flow. Surgical treatment involves the surgical repair of a narrowed or occluded artery. The basic principle of balloon angioplasty is to deliver a small balloon through a catheter into the patient's blood vessels and then inflate the narrowed vessel to allow local dilation and thus patency[16]. The procedure is similar to the principle of ballooning and requires only a small incision to complete the treatment. This method causes little to no damage to the patient's body and recovery is rapid, and it has the advantages of being safe, convenient and economical. However, due to the stimulation of the body by the intraluminal operation, the local blood vessel wall is damaged to varying degrees, and the body undergoes platelet aggregation at the injury site to form thrombus through a series of physiopathological mechanisms, and inflammatory cell aggregation induces an inflammatory response in the body, etc., which may eventually cause the proliferation of vascular smooth muscle cells and narrowing of the lumen. In this study, meta-analysis showed that the rate of >50 % restenosis after standard dose as well as low dose PCB was less than that of UCB ($p<0.05$), and the rate of >50 % restenosis after standard dose PCB was less than that of low dose PCB ($p<0.05$). The analysis concluded that paclitaxel is an effective vasodilator, has an anti mitogenic effect[17], can inhibit Growth 2/ Mitosis (G2/M) phase cell division and thus inhibit the proliferation of vascular endothelial cells to reduce the incidence of restenosis. At the same time, paclitaxel can also reduce endothelial injury and inflammatory response, which can also reduce the incidence of stenosis to a certain extent. By coating paclitaxel on the balloon surface, it can effectively inhibit the incidence of postoperative restenosis in patients while dilating the blood vessels. In addition, the high rate of revascularization with end luminal treatment is questionable as a causal factor for stenosis due to the physiological peculiarities and complexity of the femoral popliteal artery. This study showed that the postoperative TLR rate was less than that of UCB with standard dose as well as low dose PCB ($p<0.05$), and the postoperative TLR rate was less with standard dose PCB than with low dose PCB, showing that PCB was also able to reduce the postoperative restenosis rate by reducing the TLR rate. In addition, PCB is able to bring paclitaxel into full contact with the site of the lesion, accelerating the penetration of the drug into the vessel wall and producing anti-inflammatory and anti-vascular endothelial proliferation effects. Some studies have shown that paclitaxel is hydrophobic[18], that is capable of producing long-term effects on cells. In summary, the efficacy of using different doses of PCB in treating patients with femoropopliteal artery occlusion is better than UCB and the standard dose is better than the low dose, but the literature included in this study covers paclitaxel doses of 3 $\mu g/mm^2$ and 2 $\mu g/mm^2$, pending further study by including more other doses.

Conflict of interests:

The authors declared no conflict of interests.

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This article was originally published in a special issue, "Transformative Discoveries in Biomedical and Pharmaceutical Research" Indian J Pharm Sci 2023:85(4) Spl Issue "159-163"