Antithrombotic treatment before and after peripheral artery percutaneous angioplasty

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Background

Peripheral arterial disease (PAD) refers to any obstructive disease of arteries other than the coronary and cerebral arteries. PAD affects approximately 20% of adults older than 55 years and is a powerful predictor of cardiovascular mortality[1,2]. About half of all people with PAD are asymptomatic, whereas about one fifth have the typical symptoms of intermittent claudication, including muscle pain due to the lack of blood supply, and a small proportion (< 10%) have more severe symptoms, i.e. muscle pain at rest and/or ischaemic ulceration or gangrene of toes, which define critical limb ischaemia. Based on the severity of the symptoms, the disease can be classified into Fontaine stages I-IV: stage I indicates the asymptomatic state, stage IIa is defined by the occurrence of intermittent claudication after a pain-free walking distance of more than 200 m, stage IIb by intermittent claudication after walking a distance of less than 200 m, stage III by pain at rest, and stage IV by the presence of ischaemic ulcers.

The progression of PAD and its local and systemic complications can be halted and reduced by lifestyle modifications (physical exercise), and medical therapy, which should include control or elimination of atherosclerotic risk factors (cigarette smoking, hypertension, diabetes mellitus, and hyperlipidaemia).

Revascularisation procedures, whether endovascular or surgical, are indicated for individuals with a lifestyle-limiting disability due to intermittent claudication or critical limb ischaemia[3]. Percutaneous transluminal angioplasty (PTA) is a well-established endovascular technique for revascularising obstructed lower limb arteries. This technique was first introduced by Dotter and Judkins, and subsequently improved by Grüntzig[4,5]. The patency of obstructed arteries is achieved by dilatation of a stenosis (i.e. a narrowing of the vessel diameter) or recanalisation of a total occlusion, using a wire-guided inflatable balloon catheter inserted into the artery. Stents are mainly applied at the aortic bifurcation or in iliac segments. Until recently stents in the femoropopliteal district were associated with a higher risk of re-occlusion because of the smaller diameter of these vessels[6]. However, the new generation of self-expanding nitinol stents or paclitaxel-coated balloons have yielded better results than those obtained with standard balloons at the femoropopliteal level[7,8].

The technical and initial clinical success of PTA of iliac stenoses exceeds 90% in all reports in the literature. This figure approaches 100% for focal iliac lesions. Nevertheless, PTA induces a prothrombotic condition: atherosclerotic plaques are disrupted and platelets aggregate at the site of the damaged arterial wall[9]. Thus, as a result of platelet aggregation, activated blood clotting in the damaged atheromatous artery and low shear stress, recurrence of arterial narrowing (re-occlusion/restenosis) is frequent[10,11].

In the initial phase after balloon and stent procedures, thrombin-antithrombin complexes (TAT), D-dimer and fibrinopeptide A levels become elevated in the plasma, demonstrating the activation of coagulation. This condition favours early thrombotic occlusion, where 'early' is usually defined as a period covering the first 4 weeks after the intervention[12,13]. Subsequently, intimal hyperplasia, redundant healing of the arterial wall which is responsible for restenosis and re-occlusion in the mid- and long-term, may follow. Intimal hyperplasia occurs as a result of denudation (tearing off of the inner lining) of the endothelium caused by damage to the vessel wall with the catheter. Smooth muscle cells in the medial layer

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are stimulated to grow and migrate into the intimal layer[14,15].

Anatomical factors also affect the patency rate after PTA. Factors with a negative influence include the severity of the disease in run-off arteries, length of diseased segments, the number of lesions treated, stage of disease and the presence of cardiovascular risk factors[16]. Female gender has also been suggested to be associated with decreased patency of external iliac artery stents. Inflammation, revealed by an elevated C-reactive protein level, was reported to be a risk factor for restenosis at 6 months after successful femoral and popliteal PTA[17]. The estimated patency rate is much more favourable for supra-inguinal (aorto-iliac) than infra-inguinal (femoropopliteal) arteries.

The primary patency rates of the iliac artery after PTA, estimated from weighted averages (range) from reports on interventions to 2,222 limbs of patients mainly affected by intermittent claudication (76%) are 86% at 1 year, 82% at 3 years and 71% at 5 years[16]. The rate of re-occlusion or restenosis after femoropopliteal PTA is between 5 and 25% for early events and about 40% at 1 year[18]. The 5-year patency rate was reported to be 58% for femoropopliteal PTA, although patients whose stenosis or occlusion was less than 3 cm long had a higher long-term patency rate of 74%[16,19].

Patients subjected to local thrombolysis show higher incidences of restenosis/re-occlusion[20]. It is, therefore, of pivotal importance to define the lesion suitable for PTA in both the supra-inguinal and infra-inguinal districts.

The implantation of nitinol stents, drug-eluting stents, paclitaxel-coated angioplasty balloons or treatment by intravascular brachytherapy following PTA have been considered as interventions with the capacity of reducing the occurrence of restenosis/re-occlusion. A recent study by Schillinger, showed better 1-year results with self-expanding nitinol stents in femoropopliteal segments[7,21]. The safety and efficacy of immediately bioavailable, local paclitaxel for the prevention of restenois in the superficial femoral and popliteal arteries after PTA were evaluated in the THUNDER trial. The paclitaxel-coated balloon was associated with a significant reduction in late lumen loss[8]. Endovascular brachytherapy has been proposed as a promising treatment modality to reduce restenosis after angioplasty. However, the phenomenon of late acute thrombotic occlusion in patients receiving endovascular brachytherapy after stenting of the femoropopliteal arteries compromises the benefits of endovascular radiation. The fact that late acute thrombotic occlusions occur immediately after stopping clopidogrel may indicate a possible rebound mechanism. Intensive and prolonged antithrombotic prophylaxis is probably indicated in these patients[22,23].

Despite re-occlusion/restenosis being the main drawback of endovascular treatment of peripheral arteries, there are much fewer data concerning antithrombotic therapy after peripheral artery revascularisation than after coronary artery interventions. Thus, PAD patients are often treated on the basis of experience extrapolated from coronary arteries and also receive off-label combined antithrombotic therapy.

Aim

Drug interventions to prevent thrombosis and/or intimal hyperplasia leading to re-occlusion/restenosis of treated arteries would make an important improvement to the outcome of peripheral endovascular revascularisation. The main issues to consider concerning such drug interventions are: (i) the most effective and safest antithrombotic therapy; (ii) the duration and modality of the antithrombotic treatment; and (iii) the efficacy of dual therapy with antithrombotic drugs. The aim of this study was to review evidence on these issues.

Methods

We searched MEDLINE for articles published between January 1998 and January 2008 in English and Italian which addressed antithrombotic therapy before and after peripheral artery angioplasty, mainly reviews, and the Cochrane electronic database (January 2005). We found 20 articles from which we selected five.

Results

A Cochrane review of 14 randomised trials was conducted to determine whether any antithrombotic drug is more effective in preventing re-occlusion/restenosis after peripheral endovascular treatment. The trials included patients with symptomatic PAD treated by endovascular revascularisation of the iliac or femoropopliteal arteries. Various pharmacological interventions were analysed: anticoagulants,

antiplatelet agents and other vasoactive drug therapies were compared with no treatment, placebo, or any other vasoactive drug. Clinical end-points were re-obstruction, amputation, death, myocardial infarction, stroke and major bleeding[24].

Aspirin with or without dipyridamole. Compared to placebo, aspirin had a positive effect on reduction of occlusions up to 6 months after PTA. A 60% reduction of recurrent obstruction was found with aspirin 330 mg combined with dipyridamole as compared with placebo at 12 months of follow-up. At 6 months following endovascular treatment, a positive effect on patency was found with aspirin 50 to 100 mg combined with dipyridamole. These results were not, however, statistically significant. Aspirin/dipyridamole tended towards showing a superior effect on patency after femoropopliteal angioplasty compared with vitamin K antagonists at 3, 6, and 12 months. Aspirin 50 to 330 mg, with or without dipyridamole, started before femoropopliteal endovascular treatment, appeared to be the most effective and safest strategy, and reduced the incidence of re-occlusion at 6 and 12 months when compared with no therapy or vitamin K antagonists. Three trials showed that higher doses of aspirin had no advantage on early re-occlusion (within 1 month) and were more likely to cause gastrointestinal side effects including peptic ulcer[25-27].

Low molecular weight heparins. Peri-interventional treatment with low molecular weight heparin (LMWH) in femoropopliteal obstruction was more effective than unfractionated heparin over 6 months, without causing increased bleeding[28]. Restenosis after angioplasty is essentially due to intimal hyperplasia. LMWHs have experimentally been shown to have antiproliferative effects in addition to their antithrombotic properties[29]. Their potential to reduce restenosis remains to be established. Therefore, the hypothesis that LMWH plus aspirin is more effective than aspirin alone in reducing the incidence of restenosis/re-occlusion in patients undergoing PTA of femoropopliteal arteries was tested. Furthermore, it was investigated whether LMWHs have different effects in patients treated for intermittent claudication or critical limb ischaemia. In a randomised study by Koppensteiner et al., treatment with 2500 IU of dalteparin subcutaneously given for 3 months plus aspirin 100 mg/die versus aspirin alone after femoropopliteal PTA failed to reduce restenosis/re-occlusion at 12 months. However, dalteparin appeared to be beneficial at the 12-month follow-up in the subgroup of patients with critical limb ischaemia[30].

New antiplatelet drugs (thienopyridines, abciximab). There are few studies available on potent new antiplatelet drugs such as thienopyridines and abciximab.

Abciximab. In one study in high-risk patients with long segmental femoropopliteal interventions abciximab given intravenously tended to improve early patency[31].

Thienopyridines. The thienopyridine antithrombotic drugs, ticlopidine and clopidogrel, might be alternative antiplatelet agents to reduce platelet aggregation and blood clotting and maintain patency after endovascular procedures. A recent double-blind, randomised, placebo-controlled trial evaluated the antiplatelet effects of clodipogrel and aspirin versus placebo and aspirin after lower limb angioplasty. Platelet function was significantly suppressed in the clopidogrel group up to 30 days after endovascular intervention[32]. The same authors also evaluated whether markers of coagulation activation, D-dimer and TAT, were affected by clopidogrel in patients with intermittent claudication undergoing angioplasty. Endovascular intervention resulted in significant increases in TAT and D-dimer levels, but addition of clopidogrel to the standard antithrombotic therapy with aspirin had no effect on the levels of these markers before or after endovascular intervention[33]. The thienopyridines, ticlopidine and clopidogrel, might represent a useful alternative in cases in which aspirin is not tolerated, or as a combination therapy with aspirin when increased risk factors for re-occlusion are detected, although specific data are lacking.

Recommendations of the guidelines of the American College of Chest Physicians

Aspirin should be used before and after PTA of the peripheral arteries to reduce the incidence of peri-procedural thromboembolic events. This is a grade 1C recommendation of the guidelines of the American College of Chest Physicians[34]. Heparin during PTA is probably not necessary for interventions to large, high-flow arteries. This is a grade 1A recommendation[34].

Given the evidence that aspirin alone or in combination with dipyramidole may modify the natural history of intermittent claudication from

atherosclerosis, and that patients with PAD are at high risk of future cardiovascular events, in the absence of contraindications, life-long aspirin therapy (75-100 mg/die) should always be considered for these patients. This is a grade 2B recommendation. This recommendation is also applicable to all patients with PAD undergoing lower limb PTA, with or without stenting (grade 1C)[34,35].

Dual antiplatelet therapy

Platelet activation and aggregation after PTA of atherosclerotic arteries are important risk factors for re-occlusion/restenosis after endovascular procedures. Recent trials using clopidogrel, which interferes with the ADP pathway, seem to be giving promising results, particularly when clopidogrel is combined with aspirin. The benefit of more potent platelet inhibition with dual therapy, aspirin and clopidogrel, was recently demonstrated in a trial on acute coronary syndromes (CURE). The Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization (CAMPER) study was started in the United States to evaluate the efficacy and safety of this dual therapy after femoropopliteal PTA. Unfortunately, the study was stopped because of insufficient randomisation numbers. This failure was probably due to the fact that many patients are already treated off-label with clopidogrel and aspirin[24,36].

Dual antithrombotic therapy with aspirin plus ticlopidine improved the outcome after stent implantation in patients with PAD compared with the outcome in patients taking aspirin alone or aspirin plus full anticoagulation with heparin and warfarin. Because clopidogrel has the same mechanism of action as ticlopidine, but is associated with fewer side effects, it has replaced ticlopidine in clinical practice[37].

A recent Cochrane review, based on available evidence, demonstrated that, compared to aspirin alone, the use of clopidogrel plus aspirin is associated with a reduction in the risk of cardiovascular events in patients with acute non-ST coronary syndrome. In patients at high risk of cardiovascular disease but not in the acute phase, there is only weak evidence of a benefit and in fact the hazards of treatment almost match any benefit obtained[38]. The CHARISMA trial which enrolled more than 15,000 patients with either evident clinical cardiovascular disease or multiple risk factors, suggests a potential benefit of clopidogrel and aspirin versus aspirin alone in patients with symptomatic vascular disease[39]. Dual antiplatelet therapy (aspirin and ticlopidine) was also demonstrated to have a statistically significant impact on reducing adverse neurological outcomes without an additional increase in bleeding complications in patients undergoing carotid stenting[40].

Many interventionalists and angiologists have begun to use combined platelet inhibition with aspirin and clopidogrel before and after PTA and stenting in peripheral arteries. Although this strategy has not been studied in a randomised fashion, it seems to be a reasonable approach to reduce acute and subacute thrombotic complications after endovascular procedures.

Treatment 6-24 hours before the procedure with a loading dose of clopidogrel has been shown to improve the clinical outcome[41], and a 600 mg loading dose versus 300 mg at least 12 hours before the percutaneous intervention provided greater benefit in coronary syndromes[42]. In addition, patients were given an intra-arterial bolus of heparin (3000 to 5000 U) at the time of the procedure.

Dual therapy with aspirin (100 mg/die) indefinitely and clopidogrel (75 mg/die) for 4 weeks after the intervention is often adopted[8]. However, because these studies were not aimed to compare the efficacy of dual therapy with other antithrombotic drugs after PTA of peripheral arteries, further randomised, prospective studies are required.

Nevertheless, dual therapy with aspirin combined with thienopyridine should be considered for patients undergoing peripheral revascularisation, especially of femoral and more peripheral arteries[8,34]. Some issues regarding the use of clopidogrel remain unresolved, such as the optimal loading dose in patients undergoing endovascular revascularisation and the optimal duration of dual therapy following PTA and stents[43].

Conclusions

There is evidence suggesting that patients undergoing PTA benefit from receiving aspirin at a dose of 75 mg to 100 mg/die, started before the intervention and continued life-long. Thienopyridines, e.g. clopidogrel, might represent a useful alternative in cases in which aspirin is not tolerated, or as a combination therapy with aspirin, especially when increased risk factors for re-occlusion are detected, although specific data on this strategy are lacking.

The use of LMWH in selected cases (e.g. critical limb ischaemia) might be superior to unfractionated heparin for preventing early and mid-term re-occlusion/ restenosis after femoropopliteal angioplasty. Abciximab might be a useful drug for extended femoropopliteal interventions in patients at high risk of re-occlusion.

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