REVIEW

The Role of Platelets in Peripheral Vascular Disease

K. Cassar1, P. Bachoo1 and J. Brittenden2

1Vascular Unit, Ward 36, Aberdeen Royal Infirmary and 2University of Aberdeen, Aberdeen, Scotland

Platelets play a major role in acute ischaemic syndromes and peripheral vascular disease. They are involved in the development and progression of atherosclerosis, native vessel and graft thrombosis. They have a central role in the development of restenosis and reocclusion after peripheral percutaneous transluminal angioplasty. Antiplatelet therapy has been shown to be beneficial in patients undergoing peripheral vascular surgery or radiological intervention. Yet current routine therapy, namely aspirin and dipyridamole are limited in their mode of action and efficacy. Recent developments in the understanding of platelet function has led to the development of new more potent drugs such as clopidogrel. Combination of drugs and more specific investigation of individual platelet function may well result in improved bypass and angioplasty patency rates. The results of proposed large randomised controlled trials on the role and safety of aspirin and clopidogrel are awaited with interest. Given the importance of platelets in peripheral vascular disease highlighted in this review, achieving an optimal safe anti-platelet effect for each patient with peripheral vascular disease should be the target of future research.

Key Words: Platelets; Platelet activation; Platelet aggregation; Peripheral vascular diseases; Angioplasty; Platelet aggregation inhibitors.

Introduction

Platelets play a fundamental, life-saving role in haemostasis and blood clotting at sites of vascular injury. However platelet activation and arterial thrombosis are implicated in various vascular events. A large collaborative meta-analysis has shown that aspirin or another antiplatelet drug reduces the incidence of non-fatal myocardial infarction, non-fatal stroke or vascular death in patients at increased risk of occlusive vascular events.1 This implies that platelets have a major role in atherosclerosis and its complications in the coronary and cerebral vascular systems. The same disease process however is responsible for peripheral vascular disease and its complications, and platelets would also be expected to have a major role at these sites. This is supported by the findings of the Antiplatelet Trialists Collaboration2 who concluded that antiplatelet therapy reduces the odds of graft or native arterial occlusion in patients with peripheral vascular disease undergoing bypass surgery or angioplasty. This article reviews the evidence for the role of platelets in peripheral vascular disease. A Medline and PreMedline literature search (1966 to present) was performed to identify articles relating to “platelets” in combination with “peripheral vascular disease” and “peripheral arterial disease”. Further papers were identified by cross-referencing from the reference lists of relevant major articles.

The Role of Platelets in the Development and Progression of Atherosclerosis

The response-to-injury hypothesis, initially developed by Virchow in the mid-19th century, still forms the cornerstone of current understanding of the development of atherosclerosis. This has been modified by many investigators over the last 50 years, but has received a major contribution from Ross and Glomset.3–5 Injury to the arterial endothelial cell, resulting in endothelial cell dysfunction and loss, is the first step in the process of atherosclerosis. This
injury causes an immediate platelet response. Damage to the endothelium and exposure of subendothelial components, notably collagen\textsuperscript{6,7} and von Willebrand factor\textsuperscript{8} results in adherence of platelets to the damaged vessel wall and subsequent activation. Collagen interacts with glycoprotein Ia/IIa\textsuperscript{7} and vWF interacts with GPIIb/IX complex\textsuperscript{8} on the platelets resulting in adhesion of the platelets to the subendothelial matrix (Fig. 1). The binding also generates an intracellular molecular signal, in a process called “outside-in” signaling, which activates the GPIIb/IIIa receptor. This is a surface integrin receptor within the platelet membrane which undergoes a change in shape on activation to express a high-affinity binding site for fibrinogen\textsuperscript{9} (Fig. 1). This not only results in the binding of fibrinogen but once fibrinogen is bound “outside-in” signaling also occurs causing amplification of the initial signal and further platelet activation.

Platelet activation

Platelet activation also results in degranulation which involves the discharge of platelet granule contents such as the alpha-granule proteins beta-thromboglobulin, platelet factor 4 and platelet derived growth factor (PDGF) as well as adenosine diphosphate (ADP) from the platelet dense granules. PDGF is believed to play an important part in the development and progression of atherosclerosis and will be discussed later on. ADP has been recognised as an inducer of platelet aggregation since the early sixties.\textsuperscript{10,11} ADP plays a key role in platelet function because it amplifies the platelet responses induced

---

**Fig. 1.** Platelet adhesion and activation (Stages 1–3).

- **F** = Fibrinogen
- GP Ia/IIa = Glycoprotein Ia/IIa
- GPIb/IX = Glycoprotein Ib/IX
- GPIIb/IIIa = Glycoprotein IIb/IIIa
- VWF = von Willebrand Factor

1 = Endothelial denudation; binding of collagen and vWF to platelet glycoproteins
2 = Activation of GPIIb/IIIa resulting in exposure of fibrinogen binding site
3 = Binding of fibrinogen
by other platelet agonists. It also causes platelet shape change and aggregation as well as generation of thromboxane A₂, which is itself a potent platelet activator.

P-selectin which is found in the membrane of alpha granules in resting platelets rapidly appears in the outer membrane once activation occurs. This serves as a receptor for oligosaccharides within the membranes of monocytes and polymorph neutrophils causing such cells to adhere locally. The adhesion of monocytes on the lumenal surface is followed by migration across the endothelium and accumulation within the intima. Here the monocytes are converted to activated macrophages which take up lipoprotein particles and become foam cells contributing to the very early stage of atherosclerosis, the fatty streak.

**Activation of the coagulation cascade**

One of the early events after endothelial cell disruption is activation of the coagulation cascade with resultant generation of thrombin at the site of damage. This leads to further platelet activation and aggregation as well as the production of fibrin. Thrombin activates platelet aggregation at much lower concentrations than those needed to produce its coagulant effect. It binds to two protease-activated receptors termed PAR1 and PAR4. Through these receptors, thrombin activates phospholipase C which hydrolyses phosphatidylinositol 4,5 bisphosphate (PIP₂) into inositol triphosphate (IP₃) and diacylglycerol (DAG). IP₃ causes mobilisation of calcium stores which in turn activates phospholipase A₂ which leads to the production of arachidonic acid (Fig. 2). Cyclooxygenase 1 catalyses the synthesis of thromboxane A₂ from arachidonic acid in platelets leading to further platelet activation and aggregation. Aspirin exerts its anti-platelet effect by inhibiting cyclooxygenase thus preventing the synthesis of thromboxane A₂. DAG, the other product of PIP₂ hydrolysis, stimulates protein kinase C which mediates various platelet responses most important of which is activation of the fibrinogen receptor GPIIb/IIIa.

---

**Fig. 2.** Thrombin-induced platelet activation via IP₃ pathway (Stages 1–7).

Eur J Vasc Endovasc Surg Vol 25, January 2003
Proliferation of smooth muscle cells

Proliferation of smooth muscle cells is an initial and very important feature in the pathogenesis of atherosclerosis. PDGF, whose major source is circulating platelets, is a major mitogen for various cells, including the smooth muscle cell. PDGF also acts as a chemoattractant and is believed to be essential for the migration of the smooth muscle cell into the intima. Smooth muscle cells express PDGF receptors on their surface. Following the stimulation of these receptors by exogenous PDGF, smooth muscle cells commence proliferation and synthesis of a PDGF-like protein thus further stimulating mitosis.

In baboons made chronically homocystinemic, endothelial desquamation was accompanied by marked smooth-muscle proliferation. Homocystinemia, which may result in premature atherosclerosis in humans, is associated with increased production of Thromboxane A2 by platelets and subsequent platelet activation and aggregation. In a separate group of baboons treated with dipyridamole however, although there was a similar degree of endothelial desquamation, no smooth-muscle lesions developed, providing evidence of a relation between endothelial injury, platelet adhesion and smooth muscle proliferation. Similarly by using antiplatelet serum to make rabbits thrombocytopenic, the development of such lesions after balloon injury has been prevented.

Development of atherosclerosis

Evidence for the role of platelets in the development of atherosclerosis comes from observations in patients with diabetes mellitus. Diabetes is one of the major risk factors for peripheral vascular disease. Most studies have shown that platelets from patients with diabetes show a hypersensitivity to aggregating agents. There is also evidence to indicate increased release of alpha granule contents in vivo in diabetic patients and increased mitogenic effect of released factors. Decreased levels of PDGF within platelets in diabetics suggests increased release of alpha granules in this group of patients. Platelets from diabetics also show enhanced activity of the arachidonate pathway and increased prostaglandin and thromboxane A2 formation. Fibrinogen
binding to platelets from diabetic subjects is also enhanced compared to platelets from control subjects. The increased platelet activity correlates with the enhanced vascular disease in the diabetic population.

Our own group has shown, using whole blood flow cytometry, that P-selectin expression on platelets as well as platelet fibrinogen binding is increased in patients with peripheral vascular disease (work submitted for publication). This suggests that platelet activation is enhanced in patients with peripheral vascular disease compared to healthy controls.

The Role of Platelets in Thrombosis in Native Vessels

Thrombosis often occurs at sites of atherosclerotic plaque resulting in acute ischaemia of the lower limb and potentially thromboembolic episodes. Local platelet thrombosis occurs as a result of activation of platelets due to higher shear stress or more commonly fissuring or ulceration of the plaque. Shear force is directly proportional to flow velocity and is inversely proportional to the third power of the diameter of the vessel. Thus shear force is higher at sites of stenosis induced by atherosclerotic plaque which tends to develop at sites where major arteries branch or curve. Shear-induced platelet aggregation is initiated by binding of soluble vWF to platelet GPIb. Once a threshold shear is reached, the vWF-GPIb interaction triggers intracellular signaling that leads to platelet activation and binding of fibrinogen to GPIIb/IIIa with subsequent platelet aggregation.

The lipid core of advanced atheromatous lesions is rich in tissue factor which is probably generated by activated macrophages within the plaque. Disruption of these advanced plaques with exposure of their lipid cores triggers the formation of thrombus six times larger than those generated by other components of the arterial wall. Tissue factor initiates the coagulation cascade by interacting with factor VII and subsequently activating factor X. The end product of the coagulation cascade is thrombin which is itself a potent inducer of platelet aggregation. Toschi and colleagues have shown a positive correlation between quantitative platelet deposition and tissue factor in human arterial segments exposed to high shear stress in vitro. The deposition of platelets and formation of platelet aggregates leads to the occlusion of vessels. There is strong evidence to suggest that thrombus formation stimulates smooth muscle cell migration and proliferation through the action of a number of factors liberated from the platelet rich thrombus, particularly platelet derived growth factor. Mural thrombi are later incorporated into the vessel wall resulting in organised thrombi and subsequent luminal stenosis.

The important role of platelets in the progression of peripheral arterial occlusive disease was further demonstrated in a double-blind controlled trial of 300 patients with peripheral arterial occlusive disease. These patients were followed up for two years with angiography. Administration of antiplatelet drugs (aspirin with or without dipyridamole) significantly reduced the progression of disease compared to placebo.

The Role of Platelets in Occlusion of Bypass Grafts

Deposition of platelets plays an important role in failure of synthetic grafts, in causing thrombosis, thromboembolic phenomena or promoting late graft failure through the stimulation of anastomotic neointimal hyperplasia.

Demonstration of platelet deposition

The deposition of platelets on prosthetic grafts has been demonstrated in several ex-vivo and in-vivo animal models. In humans, Goldman and colleagues showed that platelets deposited and accumulated on Dacron aortofemoral grafts by using 111-indium labelled autologous platelets. Patients who had undergone bypass procedures were followed up for up to 9 years. All grafts, regardless of age accumulated platelets and even up to 9 years post-grafting Dacron grafts continued to demonstrate platelet accumulation, although at a reduced rate. Platelet labelling has also been used to compare platelet accumulation in saphenous vein, polytetrafluoroethylene (PTFE) and Dacron femoropopliteal grafts. Isotope emissions over the graft were measured and graft thrombogenicity calculated as the daily rise over 7 days. The results were expressed as a ratio of counts over the graft compared to the contralateral leg, mean thrombogenicity index. This was greatest in the Dacron grafts, followed by PTFE. Saphenous vein was markedly less thrombogenic than either prosthetic graft, which clearly corresponds with clinical data on femoropopliteal bypass graft patency.

The marked differences observed in platelet accumulation within prosthetic and venous grafts and subsequent patency rates is due in part to the inherent anti-platelet characteristics of endothelium.

Eur J Vasc Endovasc Surg Vol 25, January 2003
Komori and colleagues showed that the presence of endothelium induces relaxation in response to aggregating platelets in porcine femoral veins.\textsuperscript{52} Endothelium is a source of PGI\textsubscript{2} which is a potent activator of adenylyl cyclase. The resultant increase in cAMP causes platelet inhibition. PGI\textsubscript{2} also inhibits PDGF released from platelets even at very low doses. Nitric oxide (NO) produced by the endothelium is a potent activator of guanylate cyclase. Platelet activation is down-regulated by NO, and PGI\textsubscript{2} and NO act synergistically to inhibit platelet aggregation.\textsuperscript{53} NO has also been shown to cause disaggregation of pre-formed platelet aggregates.\textsuperscript{54} Both PGI\textsubscript{2} and NO are also potent vasodilators.\textsuperscript{55} Activated platelets themselves produce and release various compounds, such as ADP, ATP, and serotonin, that in the presence of vascular endothelium induce self-regulatory mechanisms. These factors stimulate endothelial cells through receptor-dependent mechanisms which in turn activate phospholipase C. This induces an increase in cytosolic free calcium concentration and this activates both NO synthase and phospholipase A\textsubscript{2} resulting in increased production of NO and PGI\textsubscript{2}. Thus in the presence of functional endothelium activated platelets also initiate the production of factors that limit platelet activation and vasoconstriction.

**Effect of antiplatelet treatment on platelet deposition**

Exposure to prosthetic material or denudation of the venous endothelium during harvesting of a vein are associated with platelet adhesion and aggregation. This may be amplified by technical factors that reduce graft flow, such as intact venous valves, anastomotic stricture or poor run off leading to thrombosis. Platelet deposition at sites of endothelial denudation at the time of surgery is followed by migration of smooth muscle cells into the intima and proliferation of these cells in response to various factors, particularly PDGF. Later, synthesis and deposition of extracellular matrix by activated smooth muscle cells leads to a progressive increase in intimal fibrosis and a reduction in cellularity.\textsuperscript{56,57}

In a randomised double-blind controlled trial, patients undergoing femoro-popliteal bypass surgery received either placebo or a combination of aspirin and dipyridamole in the peri-operative period.\textsuperscript{58} Using a platelet labelled technique the graft load of platelet aggregation was measured at 7 days post-op. The combination of aspirin and dipyridamole significantly reduced platelet accumulation in Dacron and PTFE grafts. Vein grafts, however, accumulated very few labelled platelets and the combination of aspirin and dipyridamole had no further effect on platelet accumulation.

This would only be of clinical importance if increased platelet deposition measured shortly after surgery was related to subsequent graft thrombosis. The relationship between platelet deposition and patency in small calibre arterial graft in patients undergoing femoropopliteal bypass has been investigated by Goldman and colleagues.\textsuperscript{59} The Dutch Bypass Oral anticoagulants or Aspirin study showed that aspirin was better for the prevention of non-venous graft occlusion.\textsuperscript{60} In a double-blind randomised controlled trial patients undergoing femoropopliteal bypass received either aspirin and dipyridamole or placebo.\textsuperscript{59} In the prosthetic grafts the combination of aspirin and dipyridamole not only reduced platelet accumulation at the graft site but was also associated with a significantly increased 1-year patency.

Further studies, including seven randomised controlled trials, have investigated the effect of antiplatelet agents in prevention of graft occlusion after infrapinguinal bypass (Table 1). Six of the seven randomised controlled trials have supported the findings of Goldman and colleagues. The 1 year cumulative patency rate for above-knee PTFE grafts was significantly higher in patients treated with aspirin alone or aspirin and dipyridamole compared to placebo in a randomised double-blind trial.\textsuperscript{61} In another prospective randomised double blind study the combination of aspirin and dipyridamole significantly increased Dacron graft patency over the first 24 months compared to placebo.\textsuperscript{62} Ticlopidine, a thienopyridine, was found to be significantly more effective at maintaining femoropopliteal or femorotibial vein graft patency than placebo in a randomised double-blind controlled trial.\textsuperscript{63} The Antiplatelet Trialists’ Collaboration concluded in their overview of randomised trials that antiplatelet therapy produced an absolute reduction in the risk of peripheral artery or graft occlusion in patients undergoing peripheral bypass or angioplasty.\textsuperscript{2}

In a randomised multicentre trial intravenous dextran-40 was shown to be effective in maintaining early patency in difficult lower extremity bypasses (i.e. femoropopliteal bypass with poor runoff using autologous vein, femoropopliteal bypass using prosthetic grafts, and single or sequential bypasses to infrapopliteal arteries).\textsuperscript{64} Shoenfeld and colleagues later showed that this was due to the antiplatelet effect of dextran-40 and not simply due to plasma volume expansion.\textsuperscript{65} Using indium labeled platelets low molecular weight dextran was found to significantly reduce platelet deposition onto graft surfaces through a direct antiplatelet effect.\textsuperscript{66} The precise mechanism of
Table 1. Randomised controlled trials of antiplatelet agents in prevention of graft occlusion after infrainguinal bypass.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>No. of patients</th>
<th>Type of bypass</th>
<th>Drugs</th>
<th>Graft material</th>
<th>Follow-up/months</th>
<th>Graft patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green 1982&lt;sup&gt;61&lt;/sup&gt;</td>
<td>49</td>
<td>AK fempop (53); BK (47)</td>
<td>A975, A + D225, P</td>
<td>PTFE</td>
<td>12</td>
<td>Above-knee grafts significantly better with A and A + D compared to P (p &lt; 0.05)</td>
</tr>
<tr>
<td>Goldman 1983&lt;sup&gt;59&lt;/sup&gt;</td>
<td>67</td>
<td>AK fempop (34); BK (33)</td>
<td>A900 + D225, P</td>
<td>PTFE (37), Dacron (16)</td>
<td>12</td>
<td>Better with A + D compared to P (p &lt; 0.05)</td>
</tr>
<tr>
<td>Kohler 1984&lt;sup&gt;60&lt;/sup&gt;</td>
<td>100</td>
<td>AK Fem-pop (37); BK (45), Crural (18)</td>
<td>A975 + D225, P</td>
<td>Vein (70), PTFE (30)</td>
<td>24</td>
<td>No significant difference between A + D and P</td>
</tr>
<tr>
<td>Donaldson 1985&lt;sup&gt;61&lt;/sup&gt;</td>
<td>65</td>
<td>AK Fem-pop (68); BK (32)</td>
<td>A990 + D225, P</td>
<td>Dacron</td>
<td>12</td>
<td>Better with A + D compared to P (p &lt; 0.05)</td>
</tr>
<tr>
<td>Sheehan 1987&lt;sup&gt;62&lt;/sup&gt;</td>
<td>65</td>
<td>AK fem-pop (73)</td>
<td>A990 + D225, P</td>
<td>Dacron</td>
<td>60</td>
<td>Better with A + D compared to P in first 24 months (p &lt; 0.05)</td>
</tr>
<tr>
<td>McCollum 1991&lt;sup&gt;62&lt;/sup&gt;</td>
<td>549</td>
<td>AK Fem-pop (41), BK (59)</td>
<td>A600 + D300, P</td>
<td>Vein</td>
<td>36</td>
<td>Better with A + D compared to P but not statistically significant (p = 0.43)</td>
</tr>
<tr>
<td>Becquemin 1997&lt;sup&gt;62&lt;/sup&gt;</td>
<td>243</td>
<td>BK femoropopliteal (243)</td>
<td>T500, P</td>
<td>Vein</td>
<td>24</td>
<td>Significantly better with T compared to P (p = 0.02)</td>
</tr>
</tbody>
</table>

AK = above-knee; BK = below-knee; A = aspirin; D = Dipyridamole; P = placebo; PTFE = polytetrafluoroethylene; T = Ticlopidine. The number beside the abbreviation refers to the dose in milligrams per day.

The role of dextran-40 is not entirely clear but one proposed mechanism is through a reduction in vWF, which is the ligand for GPIb on the platelet surface.<sup>67</sup>

The consistent improvement in patency rates associated with adjuvant antiplatelet therapy supports the central role platelets play in the two processes leading to vascular graft failure: thrombosis and intimal hyperplasia.<sup>68</sup>

The Role of Platelets in Restenosis and Occlusion after Percutaneous Transluminal Angioplasty

Platelet adhesion is the first mechanical event that occurs after endothelial denudation induced by angioplasty. This is followed by the release of PDGF which is involved in initiating the migration of medial smooth muscle cells into the intima and their subsequent proliferation.<sup>69</sup> In a rat model of balloon angioplasty, PDGF greatly increased the intimal thickening and the migration of smooth muscle cells from the media to the intima during the first 7 days after arterial injury.<sup>25</sup> The final stage in the development of the lesion of intimal hyperplasia is replication of smooth muscle cells and secretion of extracellular matrix.<sup>70</sup>

Initial success rates of peripheral percutaneous transluminal angioplasty (PTA) have reached over 90% but subsequent failure rates remain high. The 4 year primary patency rates following PTA for aortoiliac occlusive disease has been reported in a meta-analysis to be 65% for stenoses and 54% for occlusions.<sup>71</sup> For femoropopliteal disease the patency rate four years after angioplasty is reported as 52%.<sup>72</sup> Early failure is due to occlusion following thrombosis and spasm and delayed failure occurs as a result of restenosis secondary to intimal hyperplasia. Both processes are believed to be platelet dependent.<sup>73</sup>

Angioplasty induces significant damage to the artery. In vivo analysis of human iliac stenoses by intravascular ultrasound immediately after angioplasty has shown plaque fractures and “compression” of atherosclerotic plaque.<sup>74</sup> Cracking, splitting or disruption of the intima and plaque as well as dehiscence of the intima and the plaque from the underlying media is observed after angioplasty.<sup>75</sup> The damage induced results in adhesion, activation and aggregation of platelets at the site. 51-Cr labeled platelets have been used in an animal model to demonstrate a rapid rise in platelets at the site of angioplasty within 30 min and reaching a peak at 2 h.<sup>76</sup> Thus the vast majority of platelet adhesion occurs within 2 h of angioplasty. This study also showed that the more marked the intimal dissection induced by angioplasty the greater the degree of platelet accumulation. In humans undergoing PTA, 111-indium labeled platelets have been shown to accumulate at the site of angioplasty. Increased radioactivity at the site persists even 48 h later.<sup>77</sup> Miller and colleagues used a monoclonal Fab’ antibody (S12) that is specific for the platelet membrane glycoprotein (GMP140) expressed during platelet activation and have shown that platelets are activated at the site of angioplasty. In complicated procedures platelet activation was higher compared to uncomplicated procedures.<sup>78</sup> TXA<sub>2</sub> which is produced by activated platelets increases twofold after peripheral angioplasty.<sup>79</sup>
Role of Platelets in Peripheral Vascular Disease

A markedly increased platelet accumulation at the site of angioplasty, measured using labeled platelets, was found to be strongly predictive of acute angioplasty occlusion. Patients who went on to develop restenosis were also observed to have higher platelet accumulation at the site of angioplasty although this difference failed to reach statistical significance. A similar trend was seen in the relationship between high early platelet uptake at angioplasty sites and subsequent failure in a study by Poskitt and colleagues. However only 20 patients were included in this study and no clear relationship was demonstrated.

Inhibition of platelet adhesion using aurintricarboxylic acid (ATA), a substance that inhibits platelet glycoprotein Ib-vonWillebrand factor interaction, has been shown to reduce neointimal hyperplasia after balloon arterial injury in a rabbit model. This suggests that platelet adhesion is an important step in the development of neo-intimal hyperplasia. In a randomised controlled trial of 199 patients, the combination of high dose aspirin and dipyridamole significantly reduced restenosis or occlusion 6 months after percutaneous angioplasty compared to a placebo group. In another double blind study the combination of dipyridamole and aspirin proved to be slightly more effective than aspirin alone in preventing reocclusion after percutaneous angioplasty (Table 2). This suggests that a more potent anti-platelet effect is more effective at preventing restenosis after angioplasty. The use of endovascular stents is also associated with platelet adhesion, thrombosis and occlusion. Using an animal model Parsson and colleagues showed that at the site of arterial stenting there is an increase in platelet deposition. Stent surface coating and texture appears to play a role in platelet activation and for this reason various types of coatings have been developed in attempts to reduce the thrombogenicity of stents.

Table 2. Randomised controlled trials of antiplatelet agents in prevention of reocclusion/restenosis after PTA.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Number of patients</th>
<th>Drugs</th>
<th>Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heiss 1990</td>
<td>199 A+D,P</td>
<td>High dose aspirin combined with dipyridamole was statistically more effective than placebo in preventing deterioration ($p = 0.01$)</td>
<td></td>
</tr>
<tr>
<td>Hess 1978</td>
<td>101 A+D,A</td>
<td>Aspirin combined with dipyridamole was more effective than aspirin alone in maintaining patency of angioplastied vessels (84 vs 70%)</td>
<td></td>
</tr>
</tbody>
</table>

A = Aspirin; D = Dipyridamole; P = Placebo.

Conclusions

Platelets play a major role in the development and progression of atherosclerosis, in venous and prosthetic bypass graft patency and in restenosis and occlusion after peripheral percutaneous transluminal angioplasty. There is evidence that anti-platelet treatment improves the results of bypass grafting and angioplasty. To date aspirin and dipyridamole have been the two main anti-platelet drugs investigated in this context. These drugs however have limitations in terms of mode of action and in the case of aspirin possible resistance. A recent study has suggested that only 40% of male patients with claudication show the expected effect of aspirin. Aspirin only inhibits platelets through the cylo-oxygenase pathway and the mechanism of action of dipyridamole is still controversial. Current routine anti-platelet strategies are therefore sub-optimal. Improved anti-platelet efficacy may be achieved by combining aspirin with the ADP receptor inhibitor clopidogrel. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial has shown that the combination of clopidogrel with aspirin results in a 20% relative risk reduction in cardiovascular death, non-fatal myocardial infarction and stroke in patients with unstable angina compared to aspirin alone with minimal increased side effects. The potential combined effect of aspirin and clopidogrel has not been investigated in peripheral vascular disease until now. Two large multicentre studies investigating the effect of this combination of drugs following peripheral percutaneous transluminal angioplasty and peripheral bypass grafting are about to commence. Given the importance of platelets in peripheral vascular disease highlighted in this review, achieving an optimal safe anti-platelet effect for each patient with peripheral vascular disease should be the target of future research.

References

14 K. Cassar et al.


7 Nakamura T, Kamaya Y, Okuma M, Tandon NN. Activation of the GPI|IIb/IIIa complex induced by platelet adhesion to collagen is mediated by both alpha2b-integrin and GPIVI. J Biol Chem 1999; 274: 11987–11993.


Role of Platelets in Peripheral Vascular Disease


Accepted 5 October 2002