Anti-platelet therapy and Peripheral Arterial Disease

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Peripheral Arterial Disease

Population above 62 years (63% had one or more)

Cerebrovascular Disease 9%
Coronary Heart Disease 21%
PAOD 8%

Mortality

Graph showing mortality over follow-up years.
**PLATELETS**

**Rudolf Virchow**  
1821-1902

**REVIEW**

The Role of Platelets in Peripheral Vascular Disease  
K. Caesar, P. Barshou and J. Britenden

Vascular Unit, Royal Infirmary and University of Aberdeen, Aberdeen, Scotland

Platelets play a major role in acute ischaemic, thrombotic 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 athero-sclerotic lesions and associated atherosclerotic complications. Antithrombotic therapy has shown to be beneficial in patients undergoing peripheral vascular surgery or medical intervention. Anticoagulant therapy, mainly aspirin and heparinoids or derived from both routes of routes and drugs. Recent developments in the understanding of platelet function have led to the development of new drugs to change such as clopidogrel. Combination of drugs will meet specific requirements of individual patient needs and will result in improved therapy. Of note, inhibitors of platelet function are associated with increased bleeding and thrombocytopenia. Gliclazide and sulphonylurea are metabolised in the liver. Given the important role of platelets in peripheral vascular disease, highlighted in this review, achieving an optimal anti-platelet effect for each patient with peripheral vascular disease should be the target of future research.

**Endothelial Denudation**

- Endothelium
- Sub-endothelium
- Collagen
- vWF

**Platelet Adhesion**

- Endothelium
- Sub-endothelium
- Collagen
- vWF

GPIIIa/IIa

GPIIb/IIIa
Platelet Aggregation

Endothelium
Sub-endothelium
Collagen
vWF

Platelet adhesion and aggregation

Endothelium
INTIMA
IEL
MEDIA

Platelet-rich Thrombus

Vessel occlusion

Graft Occlusion

Angioplasty

Platelet-Induced Smooth Muscle Proliferation

Endothelium
INTIMA
IEL
MEDIA

PDGF
Platelet-Induced Smooth Muscle Proliferation

- Observational study: controls, claudicants, criticaals – 100 subjects
- P-selectin – marker of platelet activation

P-selectin

Resting Platelet

△ = P-selectin

Activated Platelet

△ = P-selectin

Flow Cytometer
Platelet activation - P-selectin

Results: P-selectin expression

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Claudicants</th>
<th>Criticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-selectin expression (%)</td>
<td>0.59</td>
<td>0.85 (p=0.023)</td>
<td>1.11 (p=0.028)</td>
</tr>
</tbody>
</table>

Antiplatelet Drugs

- Aspirin
- Thromboxane
- Arachidonic Acid
- GPIIb/IIIa

Joint British recommendations: 1998

- Patients with PAD should be managed in the same way as those with established coronary heart disease.

- 3123 patients with intermittent claudication in 26 trials

<table>
<thead>
<tr>
<th>Category of trial</th>
<th>No of trials with data</th>
<th>Allocated antiplatelet</th>
<th>Adjusted</th>
<th>Observed-expected</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent claudication</td>
<td>26</td>
<td>201.5123 (6.4)</td>
<td>201/149 (7.9)</td>
<td>-2.3</td>
<td>86.6</td>
</tr>
</tbody>
</table>

GP response (%)  Patient response (%)  Percentage

<table>
<thead>
<tr>
<th>Patient self-medicated</th>
<th>Patient prescribed</th>
<th>GP prescribe</th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management of secondary risk factors in patients with intermittent claudication

K Cassar, R Coull, P Bachoo, E Macaulay, J Brittenden

GP response (%)  Patient response (%)  Percentage

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The CAVA Study

A randomised, double-blind, placebo controlled trial of clopidogrel and aspirin versus aspirin alone in patients undergoing endovascular intervention for claudication

K Cassar, J Ford, M Greaves, P Bachoo, J Brittenden
Departments of Medicine and Therapeutics, and Vascular Surgery, University of Aberdeen; Vascular Unit, Aberdeen Royal Infirmary

Hypothesis

• In patients undergoing PTA/stenting clopidogrel and aspirin in combination reduce platelet activation and platelet responsiveness more effectively than aspirin alone

• Power calculation: 100 patients $p<0.05$, $\alpha=0.8$

STUDY DESIGN (double blind RCT)

100 CLAUDICANTS

randomisation

10 ASPIRIN/PLACEBO 50 ASPIRIN + CLOPIDOGREL

ANGIOPLASTY

Intervention 1

Intervention 2

Restenosis and reocclusion

Patency after SFA/pop PTA

<table>
<thead>
<tr>
<th>Immediate Success</th>
<th>1 year patency</th>
<th>2 year patency</th>
<th>3 year patency</th>
<th>4 year patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
<td>74</td>
<td>71</td>
<td>70</td>
<td>72</td>
</tr>
</tbody>
</table>

Outcome measures

- Primary
  - Platelet activation
    - Platelet P-selectin expression
    - Platelet fibrinogen binding
  - Platelet responsiveness to stimulation
    - ADP-stimulated platelet fibrinogen binding

Blood Samples

- Baseline
- 1hr pre PTA
- 1hr post PTA
- 24hr post PTA
- 30day post PTA

* = administration of loading dose of clopidogrel or placebo

Statistical Analysis

- SPSS Version 10.1
- ANOVA: mixed factorial
- P<0.05 statistically significant
- Chi-squared test/Fisher’s exact test: differences in adverse events between the two groups

Results: flow of participants

Randomised n=132

65:
(75mg Aspirin+Placebo)

67:
(75mg Aspirin + 75mg Clopidogrel)

49 Angioplasty

54 Angioplasty

No patients were lost to follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=65)</th>
<th>Clopidogrel (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males:females</td>
<td>50:15</td>
<td>52:15</td>
</tr>
<tr>
<td>Mean Age/years (Range)</td>
<td>65.4 (46-80)</td>
<td>66.1 (43-80)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>3 (4.6)</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>ex-smoker &gt; 1 year</td>
<td>27 (41.5)</td>
<td>28 (41.8)</td>
</tr>
<tr>
<td>ex-smoker &lt; 1 year</td>
<td>13 (20.0)</td>
<td>11 (16.4)</td>
</tr>
<tr>
<td>smoker</td>
<td>22 (33.8)</td>
<td>23 (34.3)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>11 (16.9)</td>
<td>12 (17.9)</td>
</tr>
<tr>
<td>Mean Serum cholesterol mmol/L (STD)</td>
<td>3.68 (2.23)</td>
<td>4.15 (2.02)</td>
</tr>
<tr>
<td>Ankle Brachial Pressure Index</td>
<td>0.63</td>
<td>0.65</td>
</tr>
</tbody>
</table>

P-selectin expression

Between subjects ANOVA P=0.03
Drop in clopidogrel group: 27-37%
Adverse Events

- No difference in bleeding complications
- No patients required surgical intervention for bleeding

Results

- Clopidogrel-aspirin combination compared to aspirin alone significantly reduces:
  - platelet activation
  - platelet responsiveness to stimulation

Conclusion

- The combination of aspirin-clopidogrel may:
  - reduce the risk of cardiovascular events
  - reduce the incidence of restenosis and reocclusion after peripheral angioplasty in claudicants
- Need for Randomised controlled trials with clinical outcome measures

Is the antiplatelet drug having an antiplatelet effect in this patient?

Aspirin Resistance
Clopidogrel resistance?

Future research

• Development of reliable simple point-of-care test of platelet function:
  – To allow correlation between platelet activation and risk of vascular events
  – to guide use of antiplatelet treatment