Problems of Plasma Replacement in TTP

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MANAGEMENT OF ACUTE TTP

• Recommendations of BCSH Guidelines B J Haem 2003; 120, 556-573 (Allford et al)
  - Single-volume daily plasma exchange should be commenced at presentation (Grade A, level Ib) and ideally within 24 h of presentation (Grade C, level IV). Plasma exchange using cryosupernatant may be more efficacious than that using FFP (Grade B, level III). Daily plasma exchange should continue for a minimum of 2 d after complete remission is obtained (Grade C, level IV).
Introduction

• The classical thrombotic lesions in TTP are
  – in the microvasculature
  – composed of platelets and von Willebrand factor

• Venous thromboembolism
  – composed mainly of fibrin
Venous thromboembolism in TTP

• The reported incidence of venous thrombosis requiring therapeutic anticoagulation in 71 consecutive TTP/HUS cases following plasma exchange therapy is 3%
  
  (Rivizi et al, Transfusion 2000 40 896-901)

• Report of 3 cases of TTP developing DVT following plasma exchange with solvent detergent plasma (Plas+SD) associated with low levels of protein S at the time of thromboses
  
  (Flamholz et al, Journal of clinical apheresis 2000 15, 169-172)
Study method

• From May 1997 - May 2002

• We retrospectively reviewed our patients with TTP with specific reference to the occurrence of VTE
Results

• 68 cases of TTP were referred for treatment or advice on management

• 8 VTE episodes were identified in 7 patients
Patient characteristics

• All patients were female
• mean age 31 years (range 24-44 years)
• 5 primary presentation of TTP
• 3 relapsed TTP
Precipitating factors for VTE

Central line 8
Pregnancy 1
Immobility 8
Obesity 3
FV Leiden heterozygosity 1
Platelet count on the day of VTE occurrence

Platelet count (x $10^9$/L)

mean =161
Day of occurrence of VTE from first plasma exchange

Mean = 53 days
Number of days of plasma exchange and component used prior to VTE

Number of days of plasma exchange

- Solvent detergent plasma
- Cryosupernatant
- Fresh frozen plasma

Patient: 1, 2, 3, 4, 5a, 5b, 6, 7
Levels of functional protein S in components

<table>
<thead>
<tr>
<th></th>
<th>Median (U/dL)</th>
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<tbody>
<tr>
<td>FFP</td>
<td>91</td>
</tr>
<tr>
<td>CSP</td>
<td>102</td>
</tr>
<tr>
<td>SD-plasma</td>
<td>58</td>
</tr>
</tbody>
</table>
Protein S levels from presentation of acute TTP for case 3
Summary

• We identified VTE in 12% of TTP cases

• 88% of these were associated with SD-plasma replacement in PEX.
WHAT TYPE OF FFP IS AVAILABLE

- Single unit, British donor standard FFP (or CSP)
- methylene blue treated/filtered single unit FFP
- solvent detergent (SD) treated pooled FFP
- psoralen S-59 and UVA light treated single unit FFP
- use of UK or non-UK plasma (male untransfused donors)
- methods in development (riboflavin)
<table>
<thead>
<tr>
<th></th>
<th>VWF:CP (%)</th>
<th>VWF:CP following overnight storage at room temperature (%)</th>
<th>VWF:Ag (IU/dL)</th>
<th>Functional PS (IU/dL)</th>
<th>Free PS:Ag (IU/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td>80-125</td>
<td>80-125</td>
<td>50-200</td>
<td>65-145 (M)</td>
<td>70-148 (M)</td>
</tr>
<tr>
<td>FFP (n=10)</td>
<td>113</td>
<td>110</td>
<td>82</td>
<td>91</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>(105-120)</td>
<td>(100-118)</td>
<td>(63-110)</td>
<td>(81-105)</td>
<td>(65-111)</td>
</tr>
<tr>
<td>CSP (n=9)</td>
<td>104</td>
<td>114</td>
<td>38*</td>
<td>102</td>
<td>110*</td>
</tr>
<tr>
<td>MB-plasma (n=10)</td>
<td>131</td>
<td>103</td>
<td>75</td>
<td>102</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>(108-144)</td>
<td>(96-120)</td>
<td>(62-123)</td>
<td>(100-120)</td>
<td>(89-110)</td>
</tr>
<tr>
<td>SD-plasma (Octaplas) (n=10)</td>
<td>99*</td>
<td>119</td>
<td>83</td>
<td>58*</td>
<td>65*</td>
</tr>
<tr>
<td></td>
<td>(94-100)</td>
<td>(111-125)</td>
<td>(71-98)</td>
<td>(56-60)</td>
<td>(63-67)</td>
</tr>
<tr>
<td>SD-plasma (Uniplas) (n=3)</td>
<td>102</td>
<td>115</td>
<td>109</td>
<td>57</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>(100-102)</td>
<td>(107-116)</td>
<td>(101-111)</td>
<td>(56-63)</td>
<td>(62-66)</td>
</tr>
</tbody>
</table>
PREVENTION OF VTE

• reduce immobility
• wear fitted full length grade II elasticated stockings
• when platelet count > 50 x 10⁹/l
  - prophylactic ASA 75mg
  - prophylactic LMW heparin high dose s/c daily
CLINICAL CHOICE OF FFP

• consider individuals risks of VTE
• initiate exchange with cryosupernatant (if available)
• median daily PEX until remission is 13 days
• remember risks of viral infection
• change to SD plasma if
  - allergic responses
  - failure to respond after 5 - 7 days
CLINICAL CHOICE OF FFP (cont’d)

• check for infected lines and remove asap
• clinical efficacy of plasma used (delayed response rate to MB treated plasma - de la Rubia et al 2001)
Conclusion

• VTE is a multifactorial disease and several known precipitating factors are present in TTP patients.

• The use of large volumes of SD-plasma in PEX may be an additional risk factor, possibly associated with protein S deficiency.

• Particularly as the median functional PS in SD-plasma is 58 U/dL compared to 91 U/dL and 102 U/dL in FFP and cryosupernatant respectively.
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