TTP: Beyond Plasma Exchange

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Faculty Discussant: Dr Jose Lopez, MD
Outline

• Case
• Standard Treatment
• Pathophysiology- new insights
• Rituximab
• N-acetylcysteine
• Patient treatment Course
• Summary
Serendipity

• “happy accident”
• “It is true that my discovery of LSD was a chance discovery, but it was the outcome of planned experiments and these experiments took place in the framework of systematic pharmaceutical, chemical research. It could better be described as serendipity” Dr Albert Hofmann
Apple tree
Case Presentation

- 48 year old female
- Confusion, subtle memory deficits
- CBC: WBC :12, Hct 41, Plt 13k, LD 1800
- WBC : 11.8, Hct 37, Plt 6k, LD 1800, Haptoglobin <10, Retic 3%, Cr 1.5, T Bilirubin 2.3
- URI x 2 weeks ago
- PMH
  - TTP: at age 33 years (1999)
  - TTP: at age 35 years (2001)
  - TTP: at age 37 years (2003) - Vincristine
  - TTP: 2004 to 2012: high dose steroids X 2 episodes
  - TTP: at age 45 years (2012) – Non ST elevation MI, CVA
Moschcowitz Syndrome/TTP

“Powerful poison which had both agglutinative and hemolytic properties”

Management

• Steroids
  Burke et al Archives of internal med 103; 1959

• Plasma- Blood transfusion
  Rubenstein et al Archives of internal med 51; 1959

• Plasma Exchange
  Rock et al NEJM 325; 1991
Case

- Started on 1 mg/kg Oral steroids
- Started Plasma exchange
- ? Anything more
Efficacy of Plasma Exchange

• Refractory
• Protracted course
• Practical concerns
• Other modalities?
“Cheese and Noodles”

- Unusually Large-vWF multimers
- vWF depolymerase
- ADAMTS-13

Effect of TTP plasma on ULVWF-cleaving activity of ADAMTS-13

Dong et al Blood 2002;100:4033-4039
“Fishing For Platelets”

- **Platelets**
  - ADAMTS13 Limiting thrombus formation by cleaving VWF
  - αβ Integrin clustered pairs at attachment sites

- **Exocytosing Weibel-Palade bodies**
  - After fusion with the plasma membrane, the coiled VWF unfurls from its tubular storage form into the flow.

Cutler Blood 2009 Feb 12;113(7)
Crawley et al. Blood 2011;118:3212-3221

TTP-Pathophysiology

Crawley et al. Blood 2011;118:3212-3221
Pasteurs Cholera Vaccine

“spoiled batch”
Rituximab

• B cell directed
• Case series
  Mischelle et al European Journal of Hematology 83 (365-372); 2009
• Retrospective analysis
Rituximab

- Cross sectional study
- 12 year follow up data
- Acquired TTP

Kaplan-Meier survival estimates of relapse-free survival.

N- Acetylcysteine

- Hypothesis: mucolytic, structural similarity
- NAC capable of reducing the size and reactivity of ULWVF

*N-acetylcysteine reduces the size and activity of von Willebrand factor in human plasma and mice. Chen et al, Journal of Clinical Investigation 2011;121(2).*
Polymeric mucins and VWF share N-terminal D domains and C-terminal C and CK domains.

NAC reduced vWF multimers

Incubation with NAC under static conditions at 37C for 30 min

Chen J, et al., J Clin Invest. 2011;121(2):593–603
NAC effect on platelet vWF strings in flow

A plots adherent to vWF strings
B Quantification of the plt-vWF strings after NAC perfusion (p < 0.001)

Chen J, et al., J Clin Invest. 2011;121(2):593–603
Cys 1272-Cys1458 disulfide bond in the vWF A1 domain

A vWF multimers by SDS and immunoblotting
B Percentage of cys 1458 in free thiol form

Chen J, et al., J Clin Invest. 2011;121(2):593–603
NAC reduced the vWF multimers in vivo in C57BL/6 mice (Wild type)

Higher doses had greater effect on multimer size

Chen J, et al., J Clin Invest. 2011;121(2):593–603
Chen J, et al., J Clin Invest. 2011;121(2):593–603
Time to thrombus resolution

(Calcium iontophore treated mesenteric vessels)

Chen J, et al., J Clin Invest. 2011;121(2):593–603
Patient data
**Patient data**

![Graph showing patient data with axes labeled as follows:
- X-axis: Hospital days (1 to 8)
- Y-axis 1: Total free thiols (folds of baseline)
- Y-axis 2: ADAMTS13 specific activity (Folds of PNP)

Key events:
- NAC infusion
- ADAMTS13 specific activity
- Rituximab
- Plasma exchange
- Discharged

Legend:
- Solid black circles: ADAMTS13 specific activity
- Open circles: Total free thiols

Graph illustrates the temporal changes in total free thiols and ADAMTS13 specific activity following interventions such as NAC infusion and Rituximab administration.
Pros
• Cheap
• Available

Cons
• Clinical data-promising
• Adverse effects
  – Nausea/vomiting/allergic reactions
  – Bleeding
A: pooled plasma  
B Purified vWF ELISA plate coated with Collagen, and bound VWF was detected with HRP conjugated vWF ab
PFA-100 device with increasing concentrations of NAC
A Collagen/ADP
B Collagen/Epi

Chen J, et al., J Clin Invest. 2011;121(2):593–603
NAC inhibits ADP and Collagen induced aggregation of platelets

Chen J, et al., J Clin Invest. 2011;121(2):593–603
Clinical data bleeding risk NAC

- Cardiac surgery patients
- Increased blood loss
- Blood utilization

*Wijeysundera et al Critical Care Medicine 2009; 37(6).*
Table 4. Adjusted association of N-acetylcysteine with large-volume blood transfusion

<table>
<thead>
<tr>
<th>Treatment Effect</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort (n = 175)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.24 (1.10–4.58)</td>
<td>0.03</td>
<td>1.85 (1.06–3.21)</td>
</tr>
<tr>
<td>Adjusted (^b)</td>
<td>3.62 (1.52–9.30)</td>
<td>0.005</td>
<td>2.07 (1.19–3.59)</td>
</tr>
<tr>
<td>Sensitivity analysis: patients who did</td>
<td></td>
<td></td>
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<tr>
<td>not receive aprotinin (n = 160)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.10 (0.99–4.46)</td>
<td>0.051</td>
<td>1.77 (0.98–3.19)</td>
</tr>
<tr>
<td>Adjusted (^b)</td>
<td>3.57 (1.45–9.52)</td>
<td>0.008</td>
<td>2.12 (1.20–3.95)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

\(^a\)≥5 units of red blood cells transfused within 24 hrs of surgery (13); \(^b\)association was adjusted for important confounders (sex, procedure, cardiopulmonary bypass time, aprotinin use). The risk-adjustment regression model had good discrimination (c-statistic 0.84) and calibration (Hosmer-Lemeshow, \(p = 0.40\)).
Summary

- Plasma Exchange
- Preemptive Rituximab
- N-Acetylcysteine: Trial
Acknowledgements

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