Activated protein C and septic shock: A propensity-matched cohort study

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Background

• PROWESS study- phase III rct NEJM -2001 – showed reduced 28 day mortality in severe sepsis by 6.1% (30.8% vs 24.7% p= .005)

• APC was approved by FDA to use in patients with severe sepsis at high risk of death.

• 90 day follow-up data from the original trial failed to demonstrate a sustained benefit

• ADDRESS study(N Engl J Med 2005)- APC in sepsis with low mortality risk showed no significant difference in 28-day mortality.
• RESOLVE study (Lancet 2007) - APC in children was stopped early after a second interim analysis suggested little benefit

• PROWESS-Shock (NEJM 2012) mortality rates of 26.4% in study group and 24.2% in control group
  – The drug was voluntarily removed from the worldwide market on October 25, 2011
• This study was conducted to determine the effectiveness of rhAPC and to identify possible reasons for the divergent results of previous trials.

• Retrospective, 2:1 propensity-matched, multicenter cohort study.

• Twenty-nine academic and community intensive care units in three countries.
• **Data Source and Study Population**
  
  – The Cooperative Antimicrobial Therapy of Septic Shock Database
  
  – Admitted to an intensive care unit (ICU) between 1997 and 2007 with a diagnosis of septic shock
Outcome Measures

• The primary outcome:
  – Mortality over 30 days
  – Mortality stratified by APACHE II quartile

• Secondary outcomes:
  – ICU and hospital mortality
  – Lengths of stay
  – Ventilator-free days,
  – Mortality stratified by time to appropriate antimicrobials and the type of infection
  – Mortality stratified by the number of organ failures on day 1 of ICU admission.
Figure 1. Patient flow through study. ICU, intensive care unit; rhAPC, recombinant human activated protein C.
• Propensity-matched analysis was undertaken for several reasons:
  – To account for the nonrandom assignment of rhAPC,
  – To mitigate potential confounding factors and selection biases,
  – and to increase statistical efficiency.
• To increase the power of the analysis, propensity matching was done using a 2:1 matching procedure where each patient of rhAPC was matched to two controls
• Mortality over 30 days was evaluated using Cox proportionalhazard model
Results:

• The mean APACHE II score in both rhAPC and control group was 26.0

• The median time to first appropriate antimicrobial after documented hypotension was 3.8 hrs in the rhAPC group and 4.3 hrs in the control group.

• The mean number of organ failures in day 1 of ICU admission was 4.2 in rhAPC group and 4.3 in the control group
• Significant reduction in mortality over 30 days (108/311 [34.7%] vs. 254/622 [40.8%])
• Subgroup analysis revealed nonsignificant reductions in mortality among all APACHE II quartiles
• Significant reductions in both ICU hospital mortality
• A time to event analysis showed that the time to appropriate antimicrobials after documented hypotension decreased for each year of study
• The use of rhAPC was associated with an increase in ICU length of stay (8/7 days) and a trend toward increased hospital length of stay (18/16 days)
• No difference in ventilator-free days.
<table>
<thead>
<tr>
<th>Septic Shock Cohort</th>
<th>Sample Size</th>
<th>Mortality Rate by Recombinant Human Activated Protein C Status</th>
<th>Mortality Rate by Control</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted^a</td>
<td>7392</td>
<td>118/349 (33.8%)</td>
<td>3017/7043 (42.8%)</td>
<td>0.75 (0.62, 0.90)</td>
<td>.002</td>
</tr>
<tr>
<td>Adjusted for propensity score^b</td>
<td>933</td>
<td>108/311 (34.7%)</td>
<td>254/622 (40.8%)</td>
<td>0.72 (0.52, 1.00)</td>
<td>.05</td>
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<tr>
<td>Stratified 30-day mortality analysis in matched cohort (Acute Physiology and Chronic Health Evaluation II quartile)</td>
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<tr>
<td>5–19</td>
<td>204</td>
<td>6/63 (9.5%)</td>
<td>31/141 (22.0%)</td>
<td>0.40 (0.17, 0.95)</td>
<td>.04</td>
</tr>
<tr>
<td>20–25</td>
<td>238</td>
<td>17/80 (21.3%)</td>
<td>49/158 (31.0%)</td>
<td>0.64 (0.37, 1.12)</td>
<td>.12</td>
</tr>
<tr>
<td>26–30</td>
<td>205</td>
<td>27/72 (37.5%)</td>
<td>53/133 (39.9%)</td>
<td>0.92 (0.58, 1.46)</td>
<td>.72</td>
</tr>
<tr>
<td>31–53</td>
<td>239</td>
<td>47/75 (64.0%)</td>
<td>111/164 (66.7%)</td>
<td>0.87 (0.62, 1.22)</td>
<td>.40</td>
</tr>
</tbody>
</table>

^aCox proportional hazard model on the unmatched cohort; ^bCox proportional hazard model using a conditional, matched-pair analysis with a shared γ-frailty model.
Figure 3. Adjusted Cox proportional hazard of mortality associated with recombinant human activated protein C (APC) in septic shock in the propensity-matched cohort.
Table 4. Secondary mortality outcomes

<table>
<thead>
<tr>
<th>Propensity-Matched Septic Shock Cohort</th>
<th>Sample Size</th>
<th>Mortality Rate by Recombinant Human Activated Protein C Status</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>No. of Deaths/Total No. of Patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital mortality</td>
<td></td>
<td>Recombinant Human Activated Protein C</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Adjusted for propensity score</td>
<td>933</td>
<td>129/311 (41.5%)</td>
<td>294/622 (47.3%)</td>
<td>0.76 (0.57, 1.00)</td>
</tr>
<tr>
<td>Intensive care unit mortality</td>
<td></td>
<td>Recombinant Human Activated Protein C</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Adjusted for propensity score</td>
<td>933</td>
<td>98/311 (31.5%)</td>
<td>232/622 (37.3%)</td>
<td>0.79 (0.63, 0.98)</td>
</tr>
<tr>
<td>30-day mortality stratified by the delay (hours) between documented hypotension and first appropriate antibiotic</td>
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<td></td>
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</tr>
<tr>
<td>0.00–1.99</td>
<td>217</td>
<td>18/70 (25.7%)</td>
<td>26/147 (17.7%)</td>
<td>1.53 (0.84, 2.78)</td>
</tr>
<tr>
<td>2–5.99</td>
<td>211</td>
<td>22/82 (26.8%)</td>
<td>42/129 (32.6%)</td>
<td>0.76 (0.46, 1.28)</td>
</tr>
<tr>
<td>6+</td>
<td>283</td>
<td>42/86 (48.8%)</td>
<td>124/197 (62.9%)</td>
<td>0.68 (0.48, 0.96)</td>
</tr>
<tr>
<td>30-day mortality stratified by infection type</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gram positive</td>
<td>305</td>
<td>35/101 (34.7%)</td>
<td>73/204 (35.8%)</td>
<td>0.93 (0.62, 1.39)</td>
</tr>
<tr>
<td>Gram negative</td>
<td>303</td>
<td>33/101 (32.7%)</td>
<td>75/202 (37.1%)</td>
<td>0.86 (0.57, 1.30)</td>
</tr>
<tr>
<td>Fungal</td>
<td>46</td>
<td>7/14 (50.0%)</td>
<td>22/32 (68.8%)</td>
<td>0.65 (0.28, 1.51)</td>
</tr>
<tr>
<td>Culture negative</td>
<td>247</td>
<td>30/85 (35.3%)</td>
<td>73/162 (45.1%)</td>
<td>0.74 (0.48, 1.13)</td>
</tr>
</tbody>
</table>

* Cox proportional hazard model using a conditional, matched-pair analysis with a shared γ-frailty model
Discussion

- This study showed mortality benefit with use of APC.
- There have been 2 other propensity matched analysis demonstrating similar benefit.
- But Prowess-shock study – a multinational phase III RCT failed to show any difference, the possible reasons for this
  - Mortality of patients with septic shock has decreased since the initial PROWESS study (which recruited patients from 1998 to 2000)
  - Availability of drug outside of a clinical setting: It is therefore possible that patients who were felt to benefit most from rhAPC received the drug off trial.
• **Strength of the study:**
  – All patients who received rhAPC during the study period were included
  – Use of a large multinational database that allowed for detailed modelling

• **Limitations:**
  – Retrospective study - unmeasured confounding variables may be present and cannot be accounted for
  – Use of propensity matching
  – Limited size
  – The lack of safety data including bleeding complications and transfusion requirements were not available
Conclusion

• Promising result of this and other propensity matched studies takes us back to 1990`s.
• There is room for further RCT and high chances of reintroduction of APC into clinical practice.