

Late Start of Surfactant Therapy and Surfactant Drug Composition as Major Causes of Failure of Phase III Multi-Center Clinical Trials of Surfactant Therapy in Adults with ARDS

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To the Editor:

We have read, with great interest, the Letter to the Editor by Grotberg et al.,⁽¹⁾ which puts forward reduced alveolar delivery as the major cause of the unexpectedly disappointing results of phase III, multi-center, controlled clinical trials of surfactant therapy in adults with acute respiratory distress syndrome (ARDS). We do hope that this will fuel a long-anticipated discussion on the causes of the failure of surfactant therapy for ARDS, despite abundant evidence from animal models with ARDS and some clinical trials that surfactant therapy is efficacious. While we strongly support Grotberg and colleagues' suggestion to further explore Grotberg's hypothesis that higher volumetric doses are needed for better drug delivery,⁽¹⁾ we would like to stress that future research cannot be limited to this one direction; for apart from studies yielding positive results of therapy with natural surfactants at a volumetric dose ranging from 2.3 ml/kg to 5.4 ml/kg,⁽²⁻⁵⁾ there are multi-center clinical trials that showed no mortality decrease in patients with ARDS despite a volumetric dose as large as 4.0 ml/kg for the drug Surfactant HL-10⁽⁶⁾ and 6-8 ml/kg for the synthetic drug Surfaxin.⁽⁷⁾ Moreover, Surfactant-BL from bovine lungs is administered at a dose of 6mg/kg and a volumetric dose of 0.5-1.0 ml/kg every 12 hours, with a mortality rate fluctuating from 14.9% to 20%.^(4,8)

There is no doubt that the efficacy of surfactant therapy is influenced by drug composition^(4,8,9) and the time when surfactant therapy is started.^(4,8,10) Tausch believes that complex natural multicomponent surfactants, which are most similar to the composition and properties of lung surfactants *in situ*, are more effective than simple surfactants.⁽⁹⁾ Synthetic

surfactant drugs, including Surfaxine, Venticute and Exosurf, are ineffective for ARDS.^(7,11,12) Design by means of modern biotechnologies of a surfactant drug with properties similar to those of the lung surfactant *in situ* is deemed unfeasible.⁽¹⁴⁾ This is in line with the fact that while surfactants used in most controlled multi-center clinical trials require a dose of 200-600mg/kg,^(6,7,11) a highly native Surfactant-BL requires a dose of only 6mg/kg when administered twice a day.^(4,8,10) The time when surfactant therapy is started is also a major factor in surfactant efficacy. In controlled multi-center clinical trials of both native and synthetic surfactants, the first dose is administered too late, within 48-72 hours after ARDS diagnosis.^(6,7,11,13) Early administration within 24 hours after PaO₂/FiO₂ decreases to less than 200 mmHg has been shown to be effective in clinical trials of Surfactant-BL, while a later administration of this drug has proved ineffective.^(4,10) Based on these data we believe that the major cause of the failure of phase III, multi-center, clinical trials of native surfactant drugs is late surfactant administration performed within 48-72 hours after patient intubation.^(2,6)

Competing interests

The authors declare that they have no competing interests.

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