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SHORT OVERVIEW OF A KEY QUESTION

Considerations for the use and study of exogenous surfactant in respiratory disease from COVID-19

Michael P. Schlegelmilch

Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

ABSTRACT

Exogenous surfactant therapy has been widely studied in acute respiratory distress syndrome (ARDS) but has failed to show mortality benefit in several trials. The COVID-19 pandemic has renewed interest in exogenous surfactant, and clinical trials are investigating surfactant therapy in COVID-19 respiratory disease. There is biological plausibility of benefit from surfactant, and patients who are early in their disease and do not meet full ARDS diagnostic criteria may respond differently, and perhaps more favourably, to surfactant therapy. Clinical trials that investigate patients with severe ARDS have a high likelihood of reproducing already known findings of surfactant therapy and systematically exclude patients who might exhibit a novel response to exogenous surfactant.

KEYWORDS

ARDS; surfactant; COVID-19

Surfactant deficiency and inactivation is implicated in the pathogenesis of acute respiratory distress syndrome (ARDS). Given this mechanism, there is a strong biologic basis to exogenous surfactant as treatment to restore the surfactant system in airways, improve aeration, ameliorate gas exchange and offer an inflammatory modulating effect.[1] Despite the plausible benefits of surfactant in ARDS, studies have failed to demonstrate a mortality benefit.[1] Several factors are hypothesized to explain why, despite the biologic plausibility, there have been disappointing results in adult trials when investigating mortality, ventilator days or ICU length of stay. Heterogeneity of patient disease, as well as surfactant preparation, dose and delivery systems likely contribute to confounding.[1]

With the emergence of SARS-CoV-2 and the ensuing COVID-19 pandemic, there is renewed interest in the application of surfactant therapy in respiratory disease.[2] SARS-CoV-2 has recently been demonstrated in murine models to exhibit a tropism for type-2 pneumocytes, which are the surfactant producing cells of the respiratory endothelium. SARS-CoV-2 infection in these mice caused surfactant loss and was associated with the development of ARDS.[3] Given these findings, the authors postulate that early administration of exogenous surfactant may reduce the severity of COVID-19 respiratory disease.[2,3]

The typical clinical syndrome of ARDS is that of atelectasis, severe hypoxia and decreased pulmonary compliance. In contrast, some cohorts of COVID-19 patients have relatively preserved lung mechanics, low recruitability and yet a high shunt fraction of around 50% leading to severe hypoxia.[4] This clinical picture has been dubbed "L-type" by Gattinoni et al.[5] and may represent a population early in their disease course and who may respond differently to exogenous surfactant therapy. These patients presumably have a relatively minimal amount of inflammation and edema, which would make the deposition of exogenous surfactant more favorable. With better airway deposition, they may have a tempering of the inflammatory cascade that ensues from direct viral cytotoxicity. There is also a theoretical antiviral benefit from exogenous surfactant. Both the lipid and protein components of surfactant have demonstrated antiviral and immune regulatory effects against other respiratory viruses, including antagonism of H1N1 influenza and selective recognition of the spike glycoprotein on SARS-CoV-1.[6,7]

The other patient group develops a respiratory syndrome that has been named the "H-type" for high pulmonary elastance, right to left shunt, lung weight and recruitability.[5] These patients meet the full criteria for ARDS and would likely have several risk factors for poor response to exogenous surfactant including pulmonary edema and mechanical obstruction of airways from mucus production and cytotoxic damage. This would make airway deposition of exogenous surfactant difficult. These patients closely resemble the "typical" ARDS patient and would likely respond in similar ways to previously studied ARDS patients with exogenous surfactant.

There are currently four clinical trials registered on *clinicaltrials.gov*, which investigate exogenous surfactant in humans with COVID-19 pneumonia (Table 1).[8] All of these trials include patients who are mechanically ventilated, some even selecting patients with severe hypoxic respiratory failure. If there is clinical and academic suspicion that an early course of surfactant may be beneficial, these trials would

CONTACT Michael P. Schlegelmilch mschlegelmilch@cheo.on.ca CHEO, 401 Smyth Road, Ottawa, Ontario K1H 8L1

Table 1. Summary of registered clinical trials for surfactant in COVID-19.

Name	Sponsor and Funding	Inclusion/Exclusion Criteria	Interventions	Outcomes
A Clinical Trial of Nebulized Surfactant for the Treatment of Moderate to Severe COVID-19 (COVSurf)	University Hospital Southampton NHS Foundation Trust Bill and Melinda Gates Foundation	*Inclusion* • COVID positive by PCR • >/=18 years • <24 hours of ventilation • Assent or professional assent *Exclusion* • Expected death < 24 hours • Surfactant contraindication • Known or suspected pregnancy • Kidney or liver failure • Anticipated transfer < 72 hours • Enrolled in other study	COVSurf surfactant delivery (nebulized) VS Standard of care	*Primary* • Oxygenation Improvement by PaO2/FiO2 • Ventilation Improvement by Ventilation Index *Secondary* • Safety Assessment of Frequency and Severity of Adverse Events
London's Exogenous Surfactant Study for COVID19 (LESSCOVID)	Lawson Health Research Institute London Health Sciences Centre (London, Ontario)	*Inclusion* • COVID positive • Age over 18 years • PaO2/FiO2 < 300 requiring intubation *Exclusion* • Known or suspected heart failure, unstable angina • Severe shock with hemodynamic instability • Severe, underlying lung disease • Concurrent treatments delivered directly to lung • Pulmonary hemorrhage	Endotracheal instillation of BLES (2 ml/kg) within 48 hours of intubation. Administered daily up to 3 doses or until extubation. VS Standard of care	*Primary* • Patient safety: worsening of oxygenation or hemodynamics • Healthcare worker safety: Respiratory • Circuit breach, or COVID-19 symptoms *Secondary* • Oxygenation by PaO2/FiO2 • Lung compliance • Ventilator days • Length of stay in ICU and Hospital • 30 day mortality • Serum levels of 10 inflammatory markers
Curosurf® in Adult Acute Respiratory Distress Syndrome Due to COVID-19 (Caards-1)	Hospital of Mantes-la-Jolie, Versailles, France	*Inclusion* • COVID positive • >18 years, ICU admission • <72 hours ventilated • ARDS by Berlin Criteria • PaO2/FiO2 ratio < 150 • Respiratory compliance < 50 mL/cmH2O *Exclusion* • Contraindication to prone • <40 kg, <140 cm or >190 cm, or obesity • Profuse bronchorrhea • Cause other than ARDS for respiratory failure • Decision to limit active therapies • No arterial line • No availability of neuromuscular blockers • Chronic organ failure • Contraindication to Curosurf or bronchoscopy • Under legal protection	Curosurf (3 ml/kg) delivered in 5 divided doses to each lobar bronchi by bronchoscopic instillation VS Standard care	*Primary* • PaO2/FiO2 at time 0, and 1 hour *Secondary* • PaO2/FiO2 at day 1 and 7 • Pulmonary compliance • 28 and 56 day survival • Mortality • Ventilator free-days • Number of prone position sessions • Time between study inclusion and last prone positioning
The Safety and Preliminary Efficacy of Lucinactant in Adults With COVID-19	Brigham & Women's Hospital, Boston, MA Duke University Windtree therapeutics	*Inclusion* • Signed and dated ICF • COVID positive by rtPCR • 18 years −75 years • Mechanical ventilation • Art line • MAP >=65 • P/F ratio <300 • Bilateral infiltrates CXR *Exclusion* • Expected death <48 hour or DNR orders • Severe lung disease (OI >/=25 or P/F < 100) • Acute coronary/ cardiac syndromes • Cardiac EF <40% • Multiple vasopressors • Cardiogenic pulmonary edema • Immune, renal, neuromuscular disease, active malignancy. • Suspected bacterial or other viral lung infection.	Lucinactant, 80 mg total phospholipids/kg of lean body weight. No control arm.	*Primary* • Oxygenation index area under the curve at 0 and 12 hours post initiation *Secondary* • Change from baseline 24 hours post dosing in: FiO2, PaO2, SpO2, PaO2/FiO2, ventilation index, and lung compliance

systematically exclude patients who are early in their illness and who may respond differently to exogenous surfactant.

Three of the 4 studies have improvement in oxygenation indices as their primary outcome. Measurements of physiologic changes are certainly of great interest; however, mortality, ventilator free days and length of ICU or hospital stay must also be reliably measured and reported. The risk to health providers of aerosolized virus exposure during surfactant treatment is not trivial and should also be closely monitored and measured.

The rapidity of the global mobilization of clinical research to COVID-19 is nothing short of incredible. The application of existing therapies to treat COVID-19 patients in novel ways is intriguing and certainly there is interest in surfactant as a therapy for COVID-19 pneumonia. However, trials must be able to measure and control for the intriguing patient heterogeneity seen in COVID-19. Investigators must consider that by selecting the most severely affected patients they may reproduce already known findings for surfactant in ARDS and systematically excluded a population who may exhibit a more novel response to exogenous surfactant therapy.

Conflicts of interest

M.P. Schlegelmilch has no conflict of interests to declare.

Author contributions

M.P. Schlegelmilch conceptualized, researched, composed and edited the manuscript.

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ORCID

Michael P. Schlegelmilch http://orcid.org/0000-0003-2175-009X

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