

CASE REPORT

Exogenous surfactant as a component of complex non-ECMO therapy of ARDS caused by influenza A virus (2009 H1N1)

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Abstract: During the pandemic caused by novel influenza A virus (subgroup H1N1), a significant number of patients became critically ill from respiratory failure. In the most severe cases of primary pneumonia, patients develop refractory hypoxemic acute respiratory distress syndrome (ARDS) with typical computed tomographic findings of multi-lobar alveolar opacities and extremely reduced pulmonary airspace. To reduce the risk of injurious ventilation and promote survival, some authors recommend the use of extracorporeal membrane oxygenation (ECMO). Unfortunately, ECMO is expensive, associated with serious complications, and available at very few centers. Other therapeutic options are clearly needed. Here we report three patients with severe influenza pneumonia who recovered following treatment with porcine surfactant (Tab. 1, Fig. 3, Ref. 6). Full Text in free PDF www.bmj.sk.

Key words: H1N1, influenza A, ARDS, surfactant.

The pulmonary presentation of severe influenza is a primary (= pulmonary) acute lung injury (ALI), or acute respiratory distress syndrome (ARDS) with radiologic findings of diffuse lung damage and significantly reduced lung volume (Fig. 1). Standard therapy for influenza pneumonia is currently antiviral chemotherapy, supportive care, and management of complications as they occur. Unfortunately, the most seriously ill patients develop such extensive lung injury that even minimally acceptable gas exchange ($\text{SaO}_2 = 90\%$ and $\text{PaCO}_2 < 9$ kPa) and protective mechanical ventilation (keeping plateau pressures < 30 to 35 cmH_2O) may be impossible to maintain (1). That means increased danger of ventilator-induced lung injury (VILI) and therefore worsening the course of the disease (2). To reduce the risk of VILI, some authors recommend the use of extracorporeal membrane oxygenation (ECMO) (3–5). Prompt initiation of ECMO therapy is emphasized. According to data from the Extracorporeal Life Support Organization, survival is approximately 72 % for patients if ECMO therapy is initiated within 6 days of intubation and only 30 % if ECMO initiation is delayed 7 or more days (5).

Here we describe three patients admitted to our department during December 2009 with refractory hypoxemic respiratory

failure and confirmed infection with 2009 H1N1 Influenza A virus. Each patient received, in addition to standard ALI/ARDS therapy, porcine surfactant. All of the patients fulfilled criteria for initiating ECMO therapy on the day of admission: Murray Lung Injury Score (Murray LIS) > 3 , hypercapnia with respiratory acidosis, plateau pressures > 30 cmH_2O , poor $\text{PaO}_2/\text{FiO}_2$ ratio and ongoing requirement for vasoactive drugs. Since ECMO was not available at the time the first patient was transferred to our department, we attempted to improve her reduced lung function by administering exogenous surfactant. This patient's apparently favorable response led us to use the same therapeutic algorithm in two other patients, who both also survived.

Case 1

This 51 year-old female was admitted to a nearby hospital following a 5-day course of fever, cough, chest pain and fatigue. Empiric antibacterial chemotherapy was started for presumed bilateral pneumonia. The following day H1N1 influenza RNA was identified in nasopharyngeal secretions using a polymerase chain reaction assay (PCR); treatment with oral oseltamivir was started. Later that day she developed worsening respiratory failure and she was transferred to the intensive care unit, where she underwent intubation and initiation of mechanical ventilation. The following day she was transferred directly to our department for further management. Low static compliance of the respiratory system (C_{RS} , 28 ml/ cmH_2O) was found (measured by Hamilton-G5 ventilator, Hamilton Medical), with $\text{PaO}_2/\text{FiO}_2$ ratio of 130. Arterial carbon dioxide pressure was elevated (PaCO_2 , 9 kPa) while keeping peak inspiratory pressure (PIP) 30 cmH_2O with arterial pH 7.23. Murray LIS was 3.5. Noradrenaline and dobutamine were infused as hemodynamic support. Computed tomography (CT) of the lung showed widespread consolidation

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Note: At the time of submitting this paper we received two more references from other regional hospitals about successful administration of surfactant in 2009 H1N1 ALI/ARDS based on our protocol.

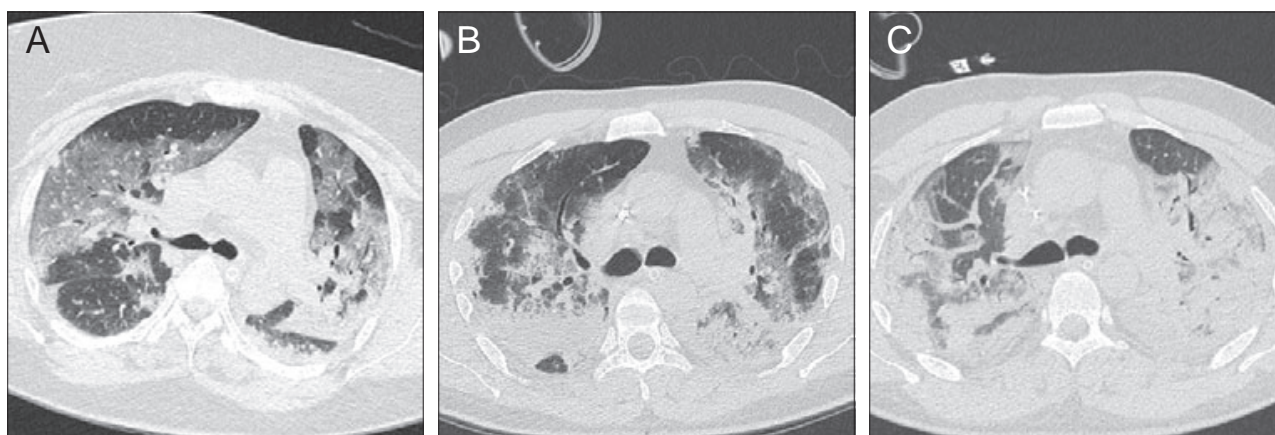


Fig. 1. CT of the lung at the time of admission to our department. Legend: A – Case 1, B – Case 2, C – Case 3.

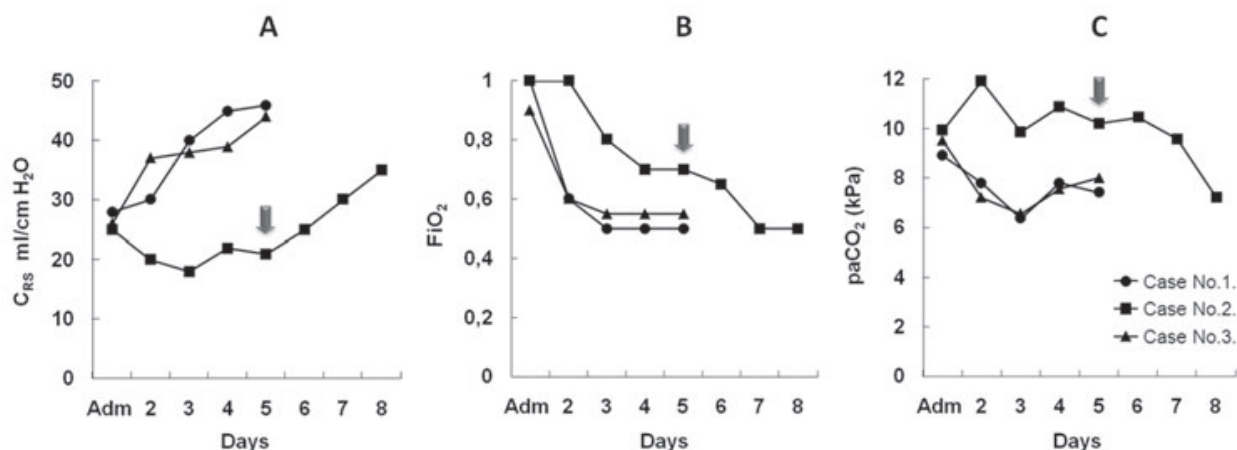


Fig. 2. The changes of respiratory variables after surfactant administration. Legend: A – static compliance of respiratory system (C_{RS}), B – inspiratory fraction of oxygen (FiO_2) needed for achievement of $SaO_2 \geq 90\%$, C – changes of arterial carbon dioxide pressure ($paCO_2$), Adm – admission to department, arrow – second administration of surfactant in Case 2.

and extensive areas of alveolar damage and ground-glass opacification (Fig. 1A). Blood gas exchange did not improve despite attempts to find the optimal protective ventilatory mode and the full supportive therapy. Due to the CT and physiological findings she met the criteria for ECMO, but it was not available. We therefore decided to administer exogenous porcine surfactant (Curosurf®, Torrex-Chiesi, description of our algorithm is available at the end of the text). During the next 5 days there was a gradual improvement in blood gases exchange and also increase in static C_{RS} (Fig. 2). A follow up CT lung scan was performed 7 days later. The calculated value of lung airspace volume (Syngo Volume Calculation, Syngo CT 2008G® Siemens) showed an increase of more than 40% compared to initial CT measured value (Fig. 3A). She gradually improved and she weaned from mechanical ventilation. At the time of submission of this report she is at home care.

Case 2

This 51 year-old male with pre-existing arterial hypertension developed fever and cough and began taking oseltamivir 3 days later. His symptoms partially improved for 4 days but subsequently worsened. He was admitted to our hospital when H1N1 influenza was identified in his nasopharyngeal secretions by PCR. Clarithromycine and amoxicillin-clavulanic acid were added concurrently to antiviral therapy. On the 3rd hospital day the antibiotic therapy was changed to meropenem and levofloxacin when his clinical course worsened. Blood markers of inflammation with exception of procalcitonin were elevated and chest X-ray findings were consistent with bilateral pneumonia. Sputum microbiologic cultures were negative. Oxygen therapy was started on hospital day 6 and mechanical ventilation on hospital day 8. One day later he was transferred to our department. As in case 1, a low C_{RS} (26 ml/cmH₂O) was found, with paO_2/FiO_2 ratio of 82.

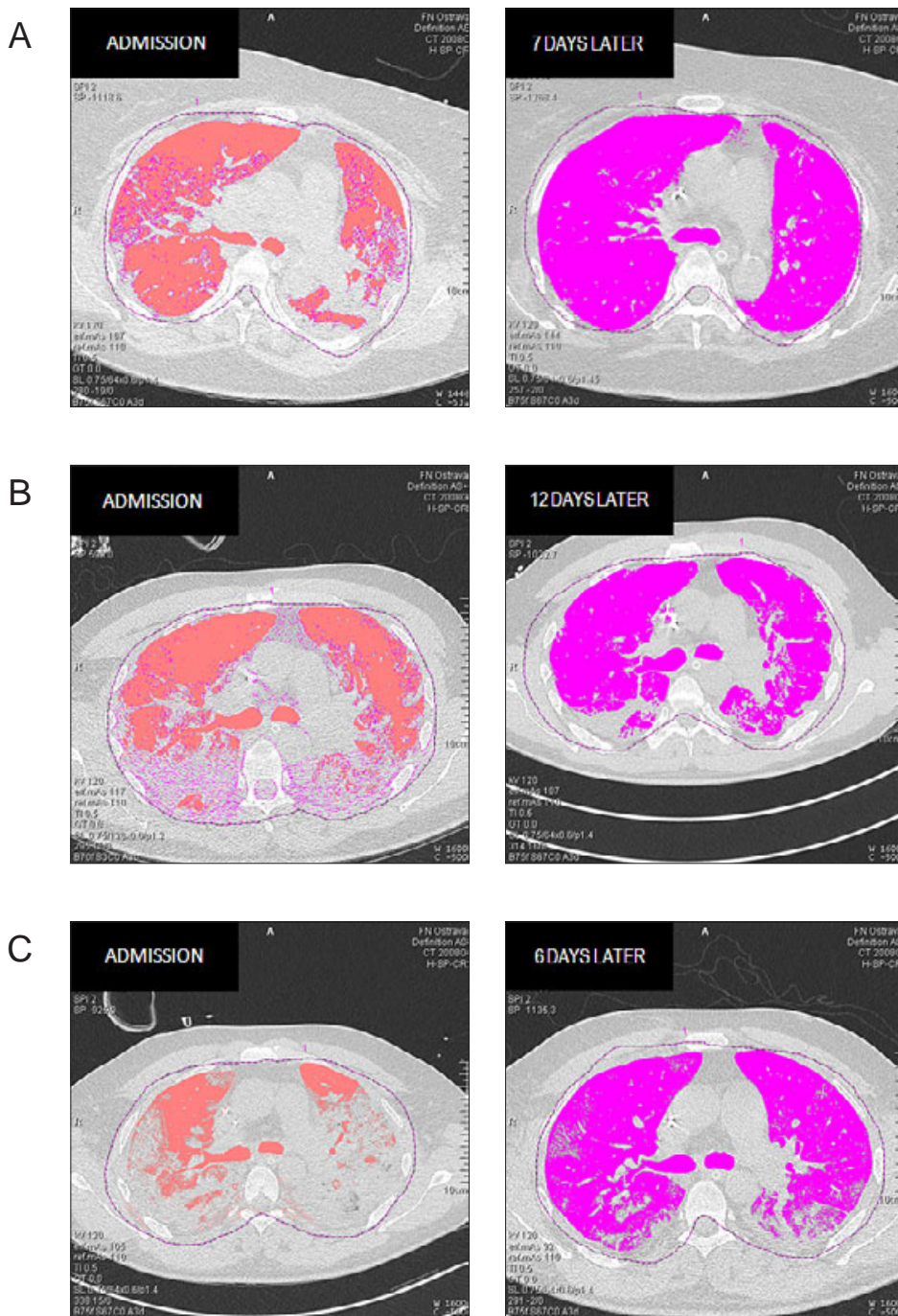


Fig. 3. The changes in CT-findings related to lung airspace volume. Legend: A – Case 1, B – Case 2, C – Case 3 (for calculation of the lung airspace value the Syngo Volume Calculation, Syngo CT 2008Gä Siemens was used).

paCO₂ was elevated (9.9 kPa) while keeping PIP 30 cmH₂O with arterial pH 7.13. Murray LIS was 3.5. Hemodynamics was supported by infusion of noradrenaline. CT of the lung again showed diffuse alveolar damage and consolidation (Fig. 1B). Surfactant was administrated shortly after the CT scan results were available. Surprisingly, there was no improvement in either C_{RS} or in

blood gas exchange, probably due to excessive systemic pro-inflammatory state (serum interleukine-6 >1000 ng/l) with increased capillary permeability and fluid leak into the lung parenchyma. Therefore, we decided to administer second dose of surfactant four days later. After the intervention there was an improvement in static C_{RS} and blood gas exchange (Fig. 2). Fol-

Tab. 1. Surfactant delivery.

Necessary conditions:

- orotracheal or tracheotomy intubation
- protective mode of mechanical ventilation
- deep analgesedation
- spiral high resolution CT of lungs (not older than 24 hours)

Algorithm:

1. stable ventilatory condition at least 30min before modified BAL is performed, adjusted FiO₂ up to 1.0
2. salbutamol nebulization 1ml (5 mg) dissolved in 3ml solution with NaCl 0.9% during 10- 20 min
3. recruitment manoeuvre (if recruitable)
4. modified BAL: HRCT-directed bronchioalveolar lavage aimed at pathologic lung areas (on segmental level) by balanced sterile solution (Hartman) prewarmed to temperature about 37° C containing low concentration of surfactant specimen 0.25 % solution - 0.2 mg/ml):
 - a. inserting endoscopic device through closed ventilatory tube system
 - b. advancing the device until it is wedged at the level of segmental bronchus
 - c. slow administration of 2x20 ml lavage fluid into each segmental bronchus, in all predetermined segments step by step, with immediate aspiration after each instillation
- d. cleaning off the maximum of the dispersed residual intrabronchial lavage fluid
5. recruitment manoeuvre (if recruitable)
6. administration of surfactant specimen into each previously lavaged segmental bronchus without aspiration of residual surfactant suspension.
Dosage per one affected segment: (25 mg x ideal body weight)/20
7. recruitment manoeuvre (if recruitable)

low up CT scan was performed 8 days after admission and a significant increase in lung volume was observed (more than 40 % compared to initial value) (Fig. 3B). The patient gradually improved, he was weaned from mechanical ventilation and then transferred to nearby hospital for further standard care. At the time of submission of this report he is back in his job without any restriction.

Case 3

This 35 year-old male was admitted to a nearby hospital following worsening of cold-like symptoms. Chest radiographs revealed bilateral infiltrates and empiric antibiotic therapy was given for presumed bacterial pneumonia. Later that day the diagnosis of H1N1 was confirmed by PCR from nasopharyngeal secretions, and oseltamivir therapy was started. On the following day he was intubated and mechanical ventilation was initiated. On the 3rd hospital day he was transferred to our department. Low C_{RS} (25 ml/cmH₂O) was found, with paO₂/FiO₂ of 100. paCO₂ was elevated (9.5 kPa) while keeping PIP 30 cmH₂O with arterial pH 7.19. Murray LIS was 3.5. Noradrenaline and dobutamine were given. CT of the lung showed diffuse alveolar damage and areas of consolidation (Fig. 1C). Surfactant was administered 7 hours after admission. There was an improvement in static C_{RS} and blood gas exchange (Fig. 2). A CT scan performed 6 days after admission showed significant increase in lung volume – in this case almost 200 % compared to initial value (Fig. 3C). The patient gradually improved and he was weaned from mechanical ventilation. At the time of submission of this report he is already at home and he is without any restriction.

Discussion

All of our patients received rescue therapy for refractory hypoxemia that included ventilator management with maximal

emphasis not to exceed PIP-value of 30 cmH₂O (permissive hypercapnia was unavoidable), inhaled nitric oxide (partial increase in paO₂ during inhalation was seen), deep sedation with intermittent administration of neuromuscular blockers, prone position (minimal effect on pulmonary functions was seen), glucocorticoids (methylprednisolone 80mg i.v. three times daily), restrictive fluid management, and appropriate antiviral and antibacterial drugs. Despite these therapeutic modalities, their clinical conditions did not substantially improve and each of them would have been treated with ECMO if it had been available. We turned to surfactant as an “alternative” to ECMO. The main reason for this was the intention to improve the mechanical lung properties allowing us to provide much protective mechanical ventilation thus preventing VILI and worsening the course of the disease (2, 6). Therefore we think it is important that we administered surfactant very early – in all cases at the day of admission to our department and up to 48 hours after mechanical ventilation was started. Moreover, we think it is important that we preceded surfactant administration by bronchoalveolar lavage (to remove surfactant inhibitors) and that we instilled the drug via bronchoscope into lung segments that were known to be densely consolidated (according to CT examination). Other aspects of our approach are outlined in Table 1. In two of the patients we found that surfactant administration was followed almost immediately by improvement in lung function, whereas in the third patient improvement followed the second dose.

Based on our observations we believe that surfactant administration was helpful in treatment of our patients. However, further research to elucidate the effect of the surfactant therapy in ALI/ARDS is needed, particularly in patients with influenza pneumonia.

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