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SURFACTANT-THERAPY OF A/H1N1 SEVERE PNEUMONIA AND ARDS IS A CHANCE FOR SURVIVAL

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Introduction

Surfactant therapy of ALI and ARDS has been studied for more than 20 years [Lachmann 1987; Spragg 2004; Rosenberg 2006].
The research was based on the following findings:

- High efficiency of surfactant therapy for RDS in newborns
- Surfactant deficiency in lavage fluid of patients with ARDS
- High efficiency of surfactant treatment in experimental animals with ALI induced by different chemical agents or lavage.

Several clinical studies of the use of surfactant formulations for ARDS showed that this approach allows to soften CMV parameters, reduce the period of CMV and reduce mortality rate from ARDS [Gregory 1997, Walmrath 2004, Willson 1999, Bautin 2002].

Surfactant-BL is a surfactant formulation produced in Russia and approved by Russian health authorities for ARDS therapy in 2003. Multi-central clinical trials demonstrated that timely (early, 1st or 2nd day of severe respiratory failure) Surfactant-BL usage with respiratory support and treatment of the main disease leads to 90% survival in patients with direct lung injury and 70-75% survival in patients with indirect lung injury [Bautin et al. 2004; Ossovskikh et al. 2003; Rosenberg 2006]. The formulation has been successfully used for 6 years for more than 1, 200 patients with sepsis, multiple trauma, severe burns of airways, massive hemotransfusion, aspiration of gastric content, complications after open heart surgery and others [Bautin et al. 2006; Rosenberg et al. 2001, 2006].

Following this experience Surfactant-BL was used for A/H1N1 severe pneumonia and ARDS treatment during the first epidemic wave of A/H1N1 in Russia in October-December of 2009.

The purpose of the study was to estimate surfactant therapy efficiency in complex treatment of severe pneumonia and ARDS caused by A/H1N1 virus.

Methods

Study enrolled 48 mechanically ventilated patients aged from 22 to 59 (21 of them were pregnant or parturient women; 9 patients had obesity of III - IV degree) with ARDS in ICU of Botkin's Hospital (Saint-Petersburg) and Perinatal Centre (Tyumen). All patients had severe bilateral confluent pneumonia and ARDS caused by A/H1N1 virus. The diagnosis was confirmed by medical history, clinical, X-ray and serological findings as well as PCR.

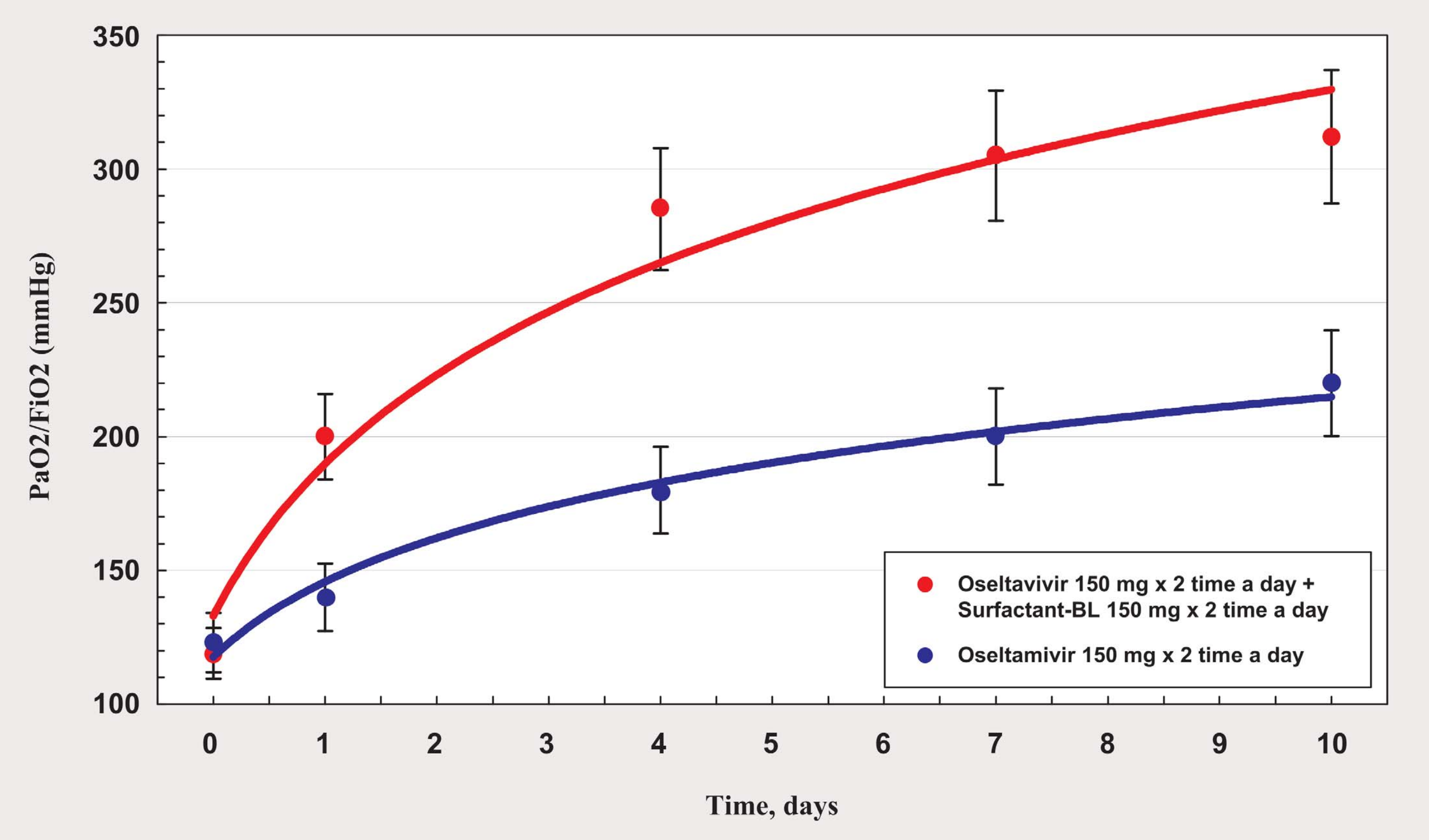
The patients were divided into 2 groups. The Group I included 23 patients, among them 12 pregnant or parturient women. The patients of this group had respiratory, antivirus (oseltamivir (F.Hoffmann La-Posh) 150 mg 2 times a day during 10 days and surfactant therapy (Surfactant-BL, Biosurf, Russia), at a dose of 150 mg, 2 times a day during 3-5 days by means of bronchofiberscope or inhalation). Group II included 25 patients of the same illness severity, among them 9 pregnant or parturient women, and the patients of Group II had the same therapy but Surfactant-BL.

Results and Discussion.

All patients had severe pneumonia. On hospitalization they were immediately delivered to ICU. The patients had dyspnea (28-34/min) with the help of ancillary muscles and PaO_2<60 mm Hg at oxygen supply of 7-10 l/min at $SatO_2 \leq 92\%$. If patients did not improve within 3 hours of that respiratory support and 4-5 days had passed from the beginning of the disease, they were transferred to invasive lung ventilation (BIPAP, CMV). Usually the CMV parameters were as following: FiO_2 = 0.8 -1.0; PEEP 14-20 cm H_2O, Pinsp=30-35 cm H_2O. During the first 2 days sedative agents and muscle relaxants (sodium oxybutyrate, benzodiazepines, pipecuronii bromide) were used because of high level of PEEP. The applied CMV parameters could not keep oxygenation level at PaO_2 > 60 mm Hg. Tracheostomy was carried out in 40% of patients. By 6-8 day in ICU the majority of patients manifested the symptoms of secondary bacterial infection (purulent excretion from bronchi, microbial analysis data). Broad spectrum antibiotics were used to fight the infection. The patients experienced leukopenia and lymphopenia. Static compliance parameter did not fall lower than 35-40 ml/cm of H_2O. X-ray data proved that all the patients had bilateral confluent pneumonia and ARDS.

The initial PaO_2/FiO_2 ratio for the patients of Group I was 119±18.2 mm Hg. 6-8 hours after the first Surfactant-BL administration at a dose of 150 mg (2.0 – 3.0 mg/kg per administration) PaO_2/FiO_2 ratio went up to 220-240 mm Hg (increasing by 100-130%), on the average up to 223±22.7 mm Hg (p<0,001). The improvement of oxygenation enabled to decrease oxygen concentration (FiO_2) to 40-50% and PEEP to 10 cm H_2O during the first 24 hours. To keep this level of oxygenation Surfactant-BL was administered at regular intervals, i.e. every 12 hours during 3-5 days. In most cases PEEP decreased to 8 cm H_2O by 2-3 day and to 5 cm H_2O by the 5th day. At the same time PaO_2 was kept at the level of 100 mm Hg and PaO_2/FiO_2 at the level of 240 mm Hg and higher (FiO_2=0.4-0.45). CMV lasted 12-30 days because of secondary bacterial hospital-acquired infection. The average duration of CMV treatment for survived patients of this group amounted to 16.0±0.89 days. In this group 1 out of 23 patients died (pregnant woman, HIV, drug addiction, stage III shock) on the 8th day after the beginning of treatment. Mortality rate in Group I was 4.3%.

PaO2/FiO2 ratio in patients with ARDS caused by A/H1N1 pneumonia. Survived patients who received oseltamivir and surfactant-BL (red line); survived patients who received only oseltamivir (blue line).

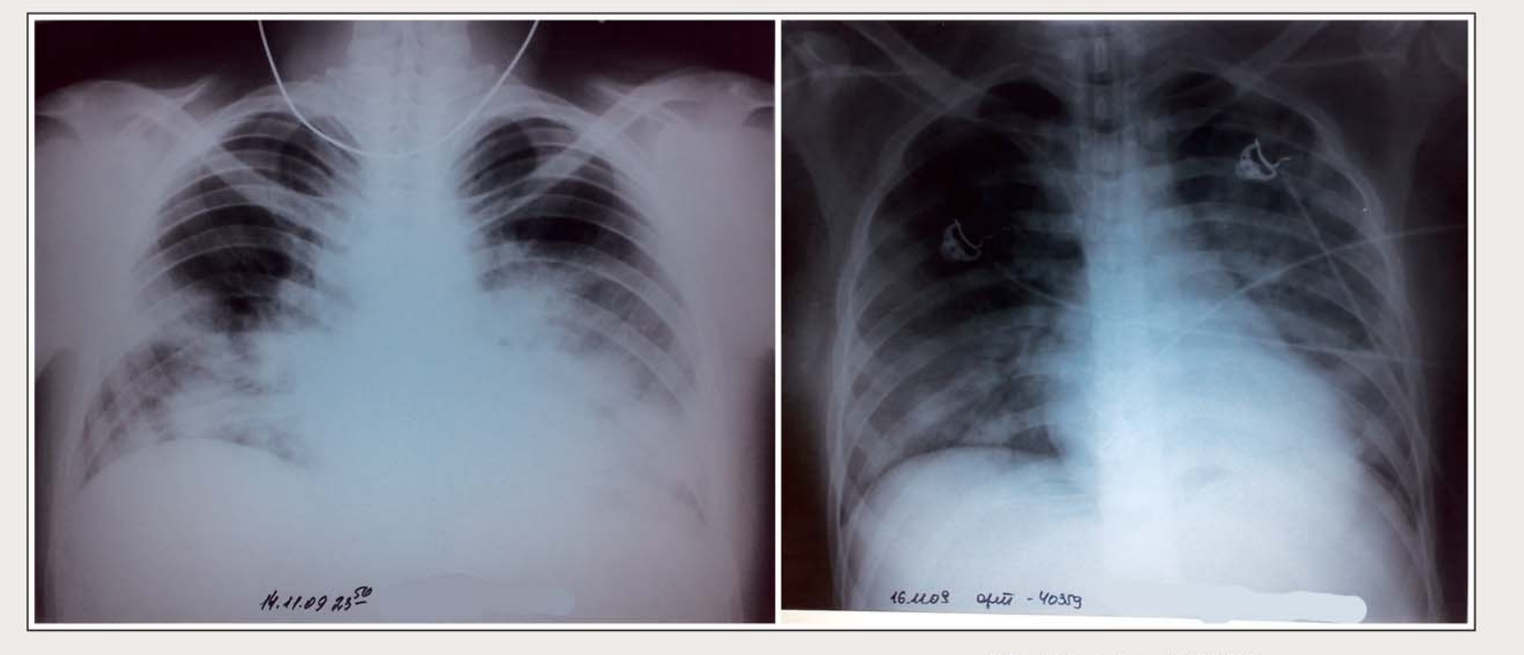


Surfactant-BL administration was carried out as early as possible, during the first day of CMV. However, the formulation showed efficiency when it was used as late as the 3-4th day of CMV.

The initial PaO_2/FiO_2 ratio for the patients of Group II when they were transfered to CMV was 123±20.8 mm Hg. During the first day of CMV PaO_2/FiO_2 ratio went up to 151±24.3 mm Hg (increasing by 22.7%, p>0.05). In this group 16 (64.0 %) out of 25 patients died. Survived patients from this group received CMV treatment during 29.3±2.8 days (P<0,001). The comparison of PaO_2/FiO_2 ratio dynamics in both groups of patients is shown in Fig. 1. Two case records of the patients of Group I are presented as illustration.

X-ray picture of the chest of patient Z, 43 year old. Before and after Surfactant-BL administration

Fig. 2

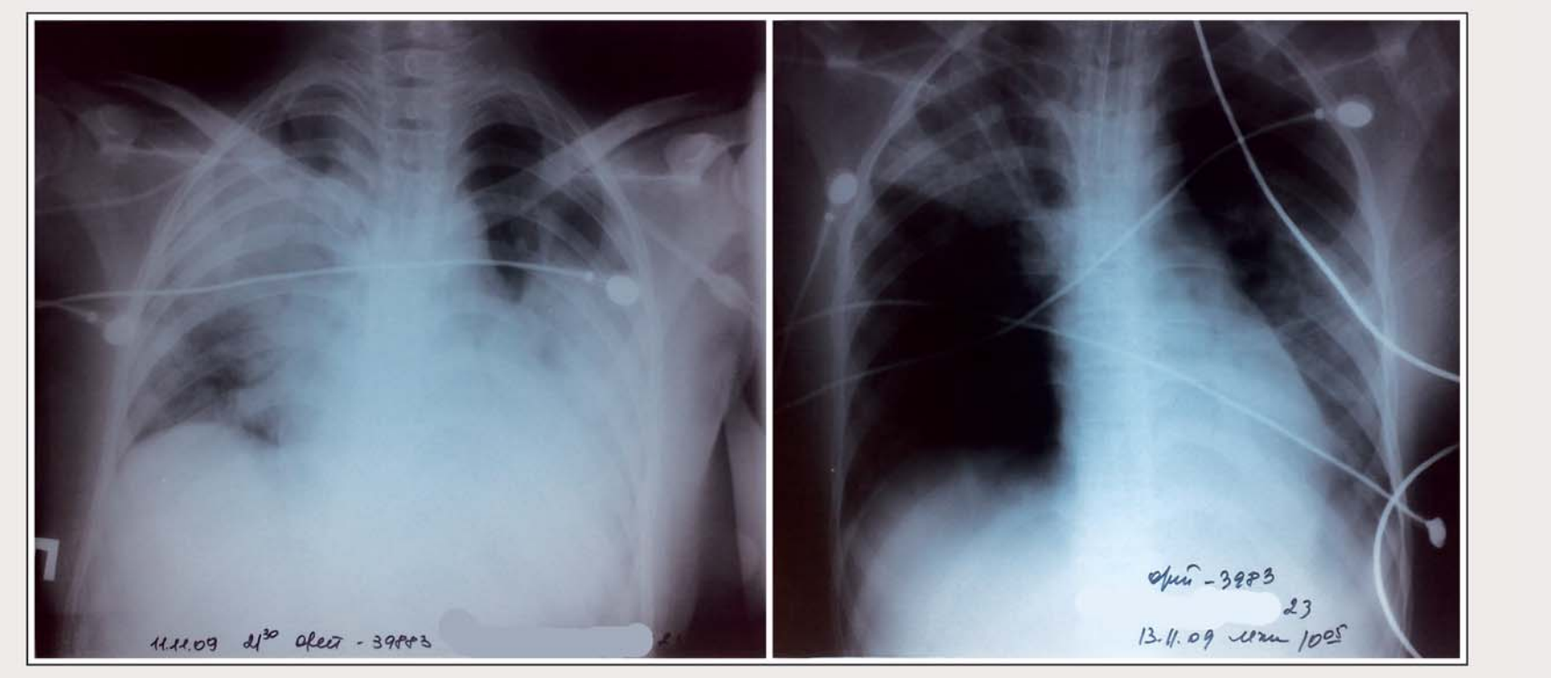


The first day of CMV before Surfactant-BL administration | The third day of CMV, 36 hours after the beginning of surfactant therapy (Surfactant-BL, 150 mg, every 12 hours)

1. ***Patient Z.*** *(F), 43 years old, was delivered to the hospital after applying to maternity welfare clinic. Diagnosis was acute respiratory viral infection; 36 weeks of pregnancy, twins (extracorporal fertilization). The patient had complained of sore throat, weakness, muscle pain, high temperature for 5 days. On hospitalization the temperature was 38,5 ^{0}C, tachypnea (30 respirations a minute), hypoxemia (SpO_2 = 87% at oxygen inhalation 7 l/min). X-ray picture demonstrated focal and confluent infiltration spreading to all lung areas. Laboratory analysis data: leukocytes 8.2 x 10^9/l, stab neutrophils - 21%, lymphocytes – 8%, increased level of C-reactive protein – 222 mg/l (norm under 5 mg/l). CMV was started. Abdominal cesarean section of alive mature fetuses was carried out as a no-choice operation. The administration of oseltamivir was started. During the 1st day the respiratory support was performed on BiPAP regime with the following parameters: PEEP = 18 cm H_2O, Pinsp= 30 cm H_2O, Tinsp =1.5 s, FiO_2 = 100%. At the same time SpO_2 was not more than 92%. At the end of the first day Surfactant-BL was administered by means of endoscope. 6 hours after administration positive dynamics was registered, PEEP level decreased to 12 cm H_2O and FiO_2 decreased to 50%; the administration of relaxants stopped; SpO_2 increased to 95-96%. Next day X-ray picture showed significant increase in lung airiness (Fig. 2). To keep the positive effect Surfactant-BL was administered during 5 days, 2 times a day at a total dose of 1500 mg (4.0 mg/kg every 24 hours). Microbial test of blood, urine and secretion from tracheobroncheal tree did not reveal any bacterial growth. PCR analysis confirmed the diagnosis of viral pneumonia. The patient was under CMV during 12 days. On the 18th day she was transferred from ICU to therapeutics unit, and on 26th day she recovered and was discharged.*

X-ray picture of the chest of patient N, 23 year old. Before and after Surfactant-BL administration

Fig. 3



The first day of CMV before Surfactant-BL administration | The third day of CMV, 36 hours after the beginning of surfactant therapy (Surfactant-BL, 150 mg, every 12 hours)

2. ***Patient N.***, *23 years old, was transferred from maternity hospital to infectious diseases hospital with the diagnosis: viral pneumonia, 37 weeks of pregnancy, threat of preterm labor, moderate anaemia. The patient had complained of sore throat, cough, dyspnea, the increase of temperature to 39 ^{0}C. On hospitalization the temperature was 39 ^{0}C, tachypnea (30 respirations a minute), hypoxemia (hemoglobin oxygen saturation 93-95% at oxygen inhalation 7 l/min). X-ray picture demonstrated disseminated inhomogeneous infiltration. Laboratory analysis data: leukocytes 2,45x10^9/l, stab neutrophils - 10%, lymphocytes – 6%, C-reactive protein – 20 mg/l. The antiviral therapy (oseltamivir) was started. At the end of the first day in hospital, respiratory failure had developed. CMV was started when SpO_2 had decreased to 90% at oxygen inhalation through mask with the flow of 9 l/min. Abdominal cesarean section was carried out as a no-choice operation. Due to increasing of gas exchange impairment during the first day the patients were on BiPAP with the following tough parameters: PEEP = 20 cm H_2O, Pinsp= 33 cm H_2O, Tinsp =1.5 s, FiO_2 = 100%. Blood gas composition: PaO_2= 41 mm Hg, $PaCO_2$ = 24 mm Hg, SpO_2 = 80%. After 2 hours of this regime Surfactant-BL (150 mg) was administered via endoscope. 6 hours after administration positive dynamics was registered, PEEP level decreased to 10 cm H_2O and FiO_2 decreased to 60%. Lung airiness increased significantly (Fig. 3). The second administration of surfactant (75 mg) was performed after 12 hours, then surfactant administration was interrupted. 24 hours after the second administration blood gas parameters were acceptable: PaO_2 = 92 mm Hg, $PaCO_2$ = 40 mm Hg, $SatO_2$ = 95%. However, the growth of hypoxemia was registered after the next 24 hours (PaO_2 = 52 mm Hg, $PaCO_2$ = 34 mm Hg, $SatO_2$ = 85%), which required to increase PEEP and FiO_2 level and use Surfactant-BL again. As a result improvement of gas exchange parameters and respiration mechanics was observed. On the 18th day of CMV the patient was weaned from it, and on 26th day she was discharged.*

In November and December 2009 at the peak of the first wave of A/H1N1 influenza in Russia, 14 hospitals in different parts of Russia and Belorussia used this method of therapy. We also possess information about another 62 patients who received antiviral therapy (Oseltamivir) and surfactant therapy (Surfactant-BL). 14 of this 62 patients received Surfactant-BL by inhalation at the very beginning of disease. Pneumonia was verified by clinical and X-ray examination, whereas the diagnosis of A/H1N1 influenza was confirmed by PCR. The patients received Surfactant-BL at a dose of 75 mg two times a day. Usually 2-3 inhalations and timely antiviral therapy led to recovery. All those 14 patients survived. 10 out of the 62 patients died (16.1%).

Ventilation parameters, PaO_2/FiO_2, CMV duration, the rate of mortality from A/H1N1 pneumonia and ARDS in complex treatment with and without surfactant.

Parameter	Initial Sat,%	Initial FiO_2	Initial PEEP, cm H_2O	Initial PaO_2/FiO_2, mm Hg	PaO_2/FiO_2 , mm Hg after 36 h at CMV	CMV duration, days	Mortality rate
Patients who received oseltamivir and Surfactant-BL	**88-92**	**0,8-1,0**	**14-20**	**119 ± 18.2**	**223 ± 22.7**	**16.0 ± 0.89**	**4.3%**
Patients who received oseltamivir only	**88-92**	**0,8-1,0**	**14-20**	**123 ± 20.08**	**151 ± 24.3**	**29.3 ± 2.8**	**64%**

Conclusion:

1. Surfactant therapy together with antiviral and respiratory therapies in complex treatment of pneumonia and ARDS caused by A/H1N1 virus is very efficient, enabling to reduce CMV parameters quickly (during 1-2 days), reduce CMV duration and decrease significantly (10 times) mortality rate from ARDS.

2. Early (on the first day of respiratory failure development) inhalation of Surfactant-BL at a dose of 75 mg per administration, 2 times a day together with antiviral therapy leads to fast pneumonia resolution and prevents ARDS development. This therapy enables to avoid invasive lung CMV.

3. Surfactant therapy in complex treatment of pneumonia and ARDS caused by A/H1N1 virus also proved efficient when Surfactant-BL was introduced into the treatment later, on the 3-4th day of CMV.

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