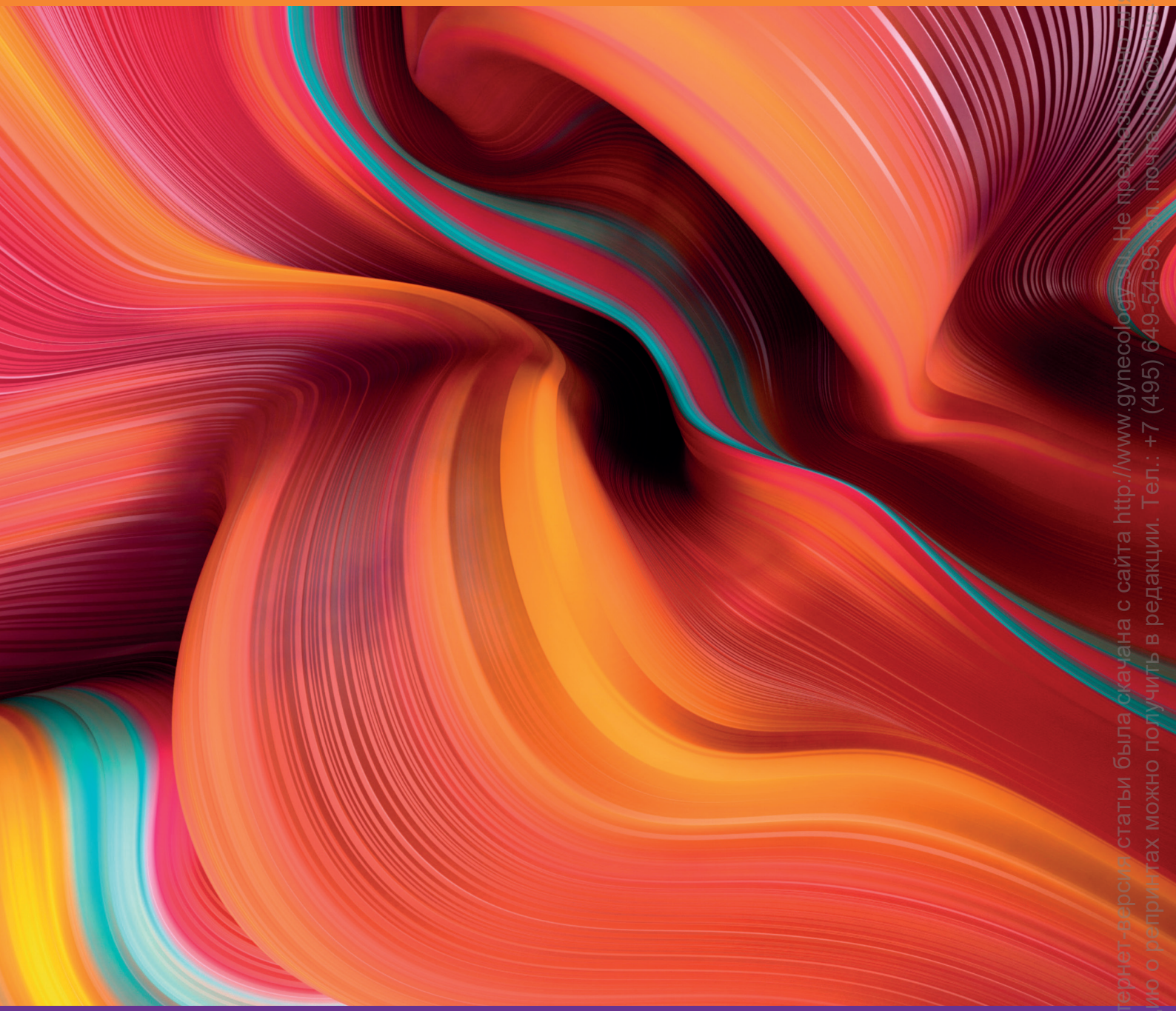
ISSN 2313-7347 (print)
ISSN 2500-3194 (online)

АКУШЕРСТВО ГИНЕКОЛОГИЯ РЕПРОДУКЦИЯ

Включен в перечень ведущих рецензируемых журналов и изданий ВАК

2023 • том 17 • № 5



OBSTETRICS, GYNECOLOGY AND REPRODUCTION

2023 Vol. 17 No 5

www.gynecology.su

ISSN 2313-7347 (print)
ISSN 2500-3194 (online)

2023 • Vol. 17 • № 5
Obstetrics, Gynecology and Reproduction

https://doi.org/10.17749/2313-7347/ob.gyn.rep.2023.448

Effect of same dose varying concentration poractant alfa on outcomes in preterm infants under 32 weeks of age

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Abstract

Introduction. We proposed a hypothesis that prognosis in preterm infants may be affected by concentration of the administered surfactant preparation able to determine its viscosity and, therefore, even distribution throughout the lungs.

Aim: to assess an effect of poractant alfa (PA) administered at low (40 mg/mL) vs. standard (80 mg/mL) concentration without changing recommended dosage (200 mg/kg) on outcomes of preterm infants at gestational age (GA) under 32 weeks receiving various respiratory support.

Materials and Methods. A prospective randomized controlled multicenter study was conducted. A total of 325 infants under 32 weeks of GA in five perinatal centers were randomized. The inclusion criteria were met by 264 patients: required respiratory therapy, had indications for surfactant administration at birth/within the first 30 minutes of life, and informed parental consent. Patients were excluded if they had no indications for surfactant preparations at the age of the first 30 minutes of life, had chromosomal and genetic abnormalities, congenital malformations, early neonatal sepsis, or gross deviations from the study protocol. Two groups were formed and compared: Low concentration (LC) group – PA concentration was 40 mg/mL (n = 111) and Standard concentration (SC) group (control) – PA concentration was 80 mg/mL (n = 153). Additionally, we compared two subgroups with surfactant preparation administered by minimally invasive methods in spontaneously breathing infants (using LISA – a less invasive method of introducing surfactant through a thin catheter or endotracheal tube): subgroup LC – PA concentration was 40 mg/mL (n = 27) and subgroup SC (control) – PA concentration was 80 mg/mL (n = 34).

Results. It was found that development of pulmonary hemorrhages in LC and SC groups was significantly less common in infants who received PA at concentration of 40 mg/mL vs. 80 mg/mL: 3.6 (4/111) % vs. 13.1 (20/153) % (p = 0.008). While comparing subgroups with minimally invasive PA administration (LISA or endotracheal tube), we found that treatment with 40 mg/mL significantly decreased total respiratory therapy duration – 142 [70.0; 219.0] hours vs. 250 [141.0; 690.0] hours (p = 0.008), incidents of bronchopulmonary dysplasia – 4.0 (1/27) % vs. 29.0 (10/34) % (p = 0.009), length of stay in neonatal intensive care unit and hospital – 8.0 [7.5; 13.0] days vs. 14.0 [8.0; 33.75] days (p = 0.014) and 38.0 [26.5; 48.5] days vs. 50.5 [36.25; 62.5] days (p = 0.014), respectively.

Conclusion. PA administered at concentration of 40 mg/mL without changing the recommended dose did not aggravate nursing of preterm infants at GA under 32 weeks. Minimally invasive PA administration at concentration of 40 mg/mL, lowered risk of bronchopulmonary dysplasia, and when used in infants on mechanical lung ventilation, it lowered a risk of pulmonary hemorrhage. All the discussed findings require to be further assessed in large prospective, multicenter, randomized studies in large patient cohort.

Keywords: pulmonary hemorrhages, bronchopulmonary dysplasia, LISA, surfactant distribution, surfactant viscosity

For citation: Mostovoi A.V., Karpova A.L., Mezhinsky S.S., Volodin N.N. Effect of same dose varying concentration poractant alfa on outcomes in preterm infants under 32 weeks of age. *Akusherstvo, Ginekologia i Reprodukcia = Obstetrics, Gynecology and Reproduction.* 2023;17(5):565–583. https://doi.org/10.17749/2313-7347/ob.gyn.rep.2023.448.

Влияние различных концентраций порактанта альфа с одинаковой дозой на исходы у недоношенных новорожденных менее 32 недель

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Резюме

Введение. Нами была выдвинута гипотеза, что на прогноз у недоношенных детей может повлиять концентрация вводимого сурфактанта, от которой будет зависеть вязкость субстанции, а следовательно, равномерность распределения в легких.

Цель: оценить влияние низкой концентрации (40 мг/мл) введенного порактанта альфа (ПА) по сравнению со стандартной концентрацией (80 мг/мл) без изменения рекомендуемой дозы (200 мг/кг) на исходы у недоношенных детей с гестационным возрастом (ГВ) менее 32 недель.

Материалы и методы. Проведено проспективное рандомизированное контролируемое многоцентровое исследование в 5 перинатальных центрах, в которое были включены 325 новорожденных со сроком гестации менее 32 недель. Критериям включения соответствовали 264 ребенка: у них была необходимость проведения респираторной терапии, показания к назначению сурфактанта при рождении/в течение первых 30 минут жизни и информированное согласие родителей. Из исследования исключались пациенты, у которых не было показаний к назначению сурфактанта в первые 30 минут жизни, с хромосомными и генетическими аномалиями, врожденными пороками развития, ранним неонатальным сепсисом или грубыми отклонениями от протокола исследования. Сравнивали 2 группы: группу «Низкой концентрации (НК)» – концентрация ПА составила 40 мг/мл (n = 111) и контрольную группу «Стандартной концентрации (СК)» – концентрация ПА составила 80 мг/мл (n = 153). Кроме того, мы дополнительно провели сравнение в двух подгруппах с введением сурфактанта малоинвазивными методами у спонтанно дышащих младенцев (с использованием метода LISA – менее инвазивного метода введения сурфактанта через тонкий катетер или эндотрахеальную трубку): подгруппа НК – концентрация ПА составила 40 мг/мл (n = 27) и подгруппа СК (контроль) – концентрация ПА составила 80 мг/мл (n = 34).

Результаты. В группах НК и СК развитие легочных кровотечений значимо реже наблюдалось у детей, получавших ПА в концентрации 40 мг/мл, по сравнению с 80 мг/мл: 3,6 (4/111) % vs. 13,1 (20/153) % (p = 0,008). При сравнении подгрупп с минимально инвазивным введением ПА (LISA или эндотрахеальная трубка) мы обнаружили после лечения 40 мг/мл статистически значимое уменьшение продолжительности общей респираторной терапии – 142 [70,0; 219,0] часа vs. 250 [141,0; 690,0] часов (p = 0,008), частоту случаев бронхолегочной дисплазии – 4,0 (1/27) % vs. 29,0 (10/34) % (p = 0,009), длительность пребывания в отделении реанимации новорожденных и в стационаре – 8,0 [7,5; 13,0] дней vs. 14,0 [8,0; 33,75] дней (p = 0,014) и 38,0 [26,5; 48,5] дней vs. 50,5 [36,25; 62,5] дней (p = 0,014) соответственно.

Заключение. Применение ПА в концентрации 40 мг/мл без изменения рекомендуемой дозы не ухудшило результаты выхаживания недоношенных детей с ГВ менее 32 недель. При малоинвазивном введении ПА в концентрации 40 мг/мл снижался риск бронхолегочной дисплазии, а при применении у детей раннего возраста, находившихся на искусственной вентиляции легких, снижался риск легочного кровотечения. Все обсуждаемые результаты требуют дальнейших крупных проспективных многоцентровых рандомизированных исследований с большим количеством пациентов.

Ключевые слова: легочное кровотечение, бронхолегочная дисплазия, LISA, распределение сурфактанта, вязкость сурфактанта

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Obstetrics, Gynecology and Reproduction

Для цитирования: Мостовой А.В., Карпова А.Л., Межинский С.С., Володин Н.Н. Влияние различных концентраций поракстанта альфа с одинаковой дозой на исходы у недоношенных новорожденных менее 32 недель. *Акушерство, Гинекология и Репродукция.* 2023;17(5):565–583. (In English). https://doi.org/10.17749/2313-7347/ob.gyn.rep.2023.448.

Highlights

What is already known about this subject?

- Viscosity is the important factor influencing a velocity, degree and uniformity of lung surfactant distribution.
- Escalating surfactant phospholipid concentration causes a naturally increased viscosity leading newly acquired properties of a non-Newtonian fluid, which flow is characterized by the viscosity/velocity gradient relation.
- Treatment effectiveness largely depends on uniformity distribution of inoculated surfactant preparation in the respiratory tract.

What are the new findings?

- A twofold increase in the volume of administered surfactant preparation does not potentiate adverse effects – episodes of hypoxia and/or bradycardia in preterm infants.
- Poractant alfa (PA) use at concentration of 40 mg/mL and total dose of 200 mg/kg in children on invasive mechanical lung ventilation lowers a risk of pulmonary hemorrhage by 4-fold.
- PA use at concentration of 40 mg/mL and total dose of 200 mg/kg in children with minimally invasive administration significantly lowers a risk of developing bronchopulmonary dysplasia as well as the overall duration of respiratory therapy.

How might it impact on clinical practice in the foreseeable future?

- Low PA concentrations (40 mg/mL) at total dose of 200 mg/kg did not adversely affect outcomes in infants under 32 weeks of gestation. A twofold increase in administered PA volume did not elevate a risk of developing hypoxemia and bradycardia as well as their severity immediately upon administration.
- Compared with PA administered at low concentration of 40 mg/mL, PA at concentration of 80 mg/mL may predispose to increased risk of pulmonary hemorrhage during mechanical lung ventilation.
- Minimally invasive surfactant administration at 40 mg/mL PA concentration and recommended dose of 200 mg/kg using LISA method neutralizes surfactant loss upon administration, promotes uniform lungs distribution and shortens duration of respiratory support.

Основные моменты

Что уже известно об этой теме?

- Вязкость является важным фактором, влияющим на скорость, степень и равномерность распределения сурфактанта в легких.
- Увеличение концентрации фосфолипидов сурфактанта вызывает естественное увеличение вязкости, приводящее к приобретению свойств неньютоновской жидкости, течение которой характеризуется зависимостью вязкости от градиента скорости.
- Эффективность лечения значимо зависит от равномерности распределения введенного сурфактанта в дыхательных путях.

Что нового дает статья?

- Двукратное увеличение объема вводимого сурфактанта не усиливает нежелательные эффекты – эпизоды гипоксии и/или брадикардию у недоношенных новорожденных.
- Применение поракстанта альфа (ПА) с концентрацией 40 мг/мл в дозе 200 мг/кг у детей на инвазивной искусственной вентиляции легких снижает риск легочного кровотечение в 4 раза.
- Применение ПА с концентрацией 40 мг/мл в дозе 200 мг/кг у детей при малоинвазивном введении значимо снижает риск развития бронхолегочной дисплазии, а также общей длительности респираторной терапии.

Как это может повлиять на клиническую практику в обозримом будущем?

- Низкая концентрация ПА в дозе 40 мг/мл в дозе 200 мг/кг не оказала негативного влияния на исходы у детей со сроком гестации менее 32 недель. Двукратное увеличение объема вводимого ПА не повышало риск развития и выраженность гипоксемии и брадикардии непосредственно в момент введения.
- ПА в концентрации 80 мг/мл может предрасполагать к повышенному риску легочного кровотечения во время искусственной вентиляции легких в сравнении с низкой концентрацией 40 мг/мл.
- Снижение концентрации за счет увеличения объема вводимого ПА с рекомендуемой дозой 200 мг/кг методом LISA нивелирует потери сурфактанта при введении, способствует равномерному распределению в легких и приведет к уменьшению продолжительности респираторной поддержки.

Introduction / Введение

Surfactant replacement therapy is based on the pathogenesis of respiratory distress syndrome (RDS), which in part is to stabilize newborn respiratory function, where surfactant therapy is essential. Surfactant therapy is an essential part of the stabilization. Surfactant therapy with poractant alfa (PA) has been studied thoroughly in numerous clinical studies which involved dose finding and timing studies [1, 2]. At the same time, the influence of some factors and drug characteristics (concentration and viscosity) on the effectiveness and clinical outcomes of newborn respiratory disorders have not been studied sufficiently. Of particular interest is the hypothesis that a high concentration of phospholipids determining exogenous surfactant viscosity may affect the pattern of

drug distribution. A non-homologous distribution may negatively affect disease course and outcome.

According to K. Cassidy et al. (2001) [3], J. Anderson et al. (2004) [4] and King D.M. et al. (2001) [5], the viscosity of a lung surfactant depends on its molecular composition, microstructure, interaction between components and environmental conditions. Viscosity was the major factor influencing a velocity, degree and uniformity of lung surfactant distribution. A relation between pulmonary surfactant viscosity and phospholipid concentration was non-linear, and increased viscosity was more pronounced at higher vs. lower concentrations. D.M. King et al. (2001) showed that rise in surfactant-related phospholipid concentration causes an intrinsically increased viscosity resulting in newly acquired properties of a non-Newtonian liquid [5], which flow is characterized by viscosity/velocity gradient relation. Usually, such liquids are highly heterogeneous and consist of large molecules [6]. By comparison, a Newtonian fluid may be of any origin that preserves fluid properties no matter what forces act on it, which is summarized in Newton's law of viscosity, exemplified by water. Viscous behavior of surfactant preparations became strongly non-Newtonian upon escalating phospholipid concentration, with larger viscosity level found at low shear rates [5]. Having acquired the properties of a non-Newtonian liquid, an exogenous surfactant, thus, has a lower fluidity, and pattern of its distribution in the respiratory tract depends on a number of physical factors, and above all on the forces of gas flow acting on the liquid during its movement.

Attempts to study the distribution of exogenous surfactant in the lungs coupled to its physical and chemical properties, were made repeatedly. F.F. Espinosa and R.D. Kamm (1998) tried in *in vitro* studies to simulate an effect of inertia forces, degree of surface tension and gravity on distribution of surfactant "plugs" [6]. It was concluded that injection rate, viscosity of the solution and tilt relative to gravity had the effect on emerging "meniscus". The latter was defined as the curve in the upper surface of a liquid next to the surface of another object caused by surface tension (**Fig. 1**).The degree of curvature of the "meniscus", in turn, determines a uniform drug distribution [6]. Using bifurcation models of the upper respiratory tract, Y. Zheng et al. (2005, 2006) [7, 8], and then A. Copploe et al. (2019) [9] confirmed an impact of gravity, surface tension and inertia on the splitting of the surfactant "plug" in the area of dichotomous division of the respiratory tract (**Fig. 1**). Treatment effectiveness largely on uniformity distribution for the injected surfactant in the respiratory tract [7–9].

Surfactant distribution at different levels of the respiratory tract occurs due to various mechanisms. The transport zone of the lungs is represented by a large number of dichotomically dividing airways, the diameter

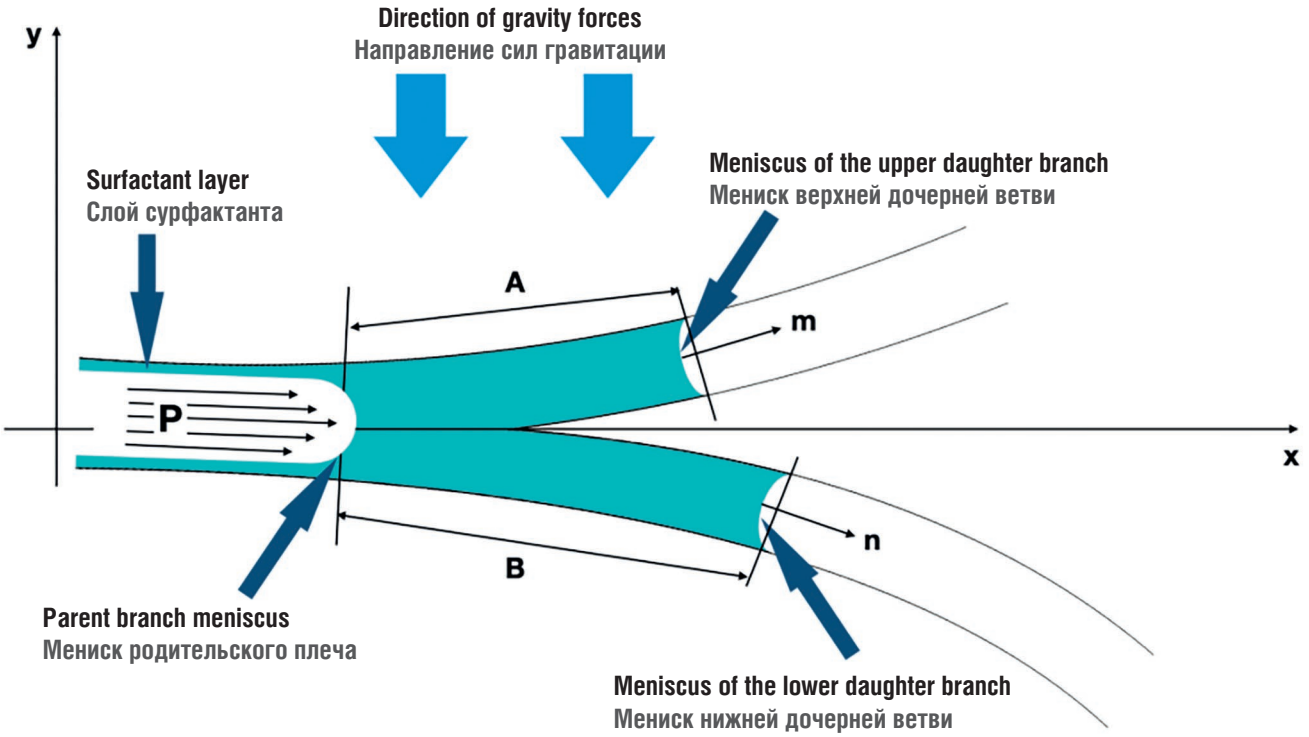

Figure 1. Influence of gravity forces, injection rate (P) and tilt (m, n) on surfactant distribution in the upper respiratory tract. In dichotomous division of the bronchus, the upper part of the surfactant (distance A) moves less than the lower part (distance B) due to the gravity action (adapted from [9]).

Рисунок 1. Влияние сил гравитации, скорости введения (P) и наклона (m, n) на распределение сурфактанта в верхних дыхательных путях. При дихотомическом разделении бронха верхняя часть сурфактанта (расстояние A) перемещается меньше, чем нижняя часть (расстояние B) за счет действия силы тяжести (адаптировано из [9]).

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of which progressively decreases in the distal direction. The distribution at the tracheal bifurcation level is rapid and depends on surfactant volumetric viscosity, a lower value of which ensures a more uniform and rapid distribution [3, 6, 10]. The distribution of exogenous surfactant in the small-diameter airways and alveoli depends more on variation in surface tension differences for diverse fluids and components in the pulmonary system (Marangoni effect). Following fairly rapid transients, on the order of seconds, a steady-state transport develops being governed by interplay between Marangoni flow and alveolar kinetics [10]. In addition, the nature of the distribution underlies differences in surface viscosity. Bulk viscosity remains poorly understood.

In 1990s, N. Gilliard et al. found that increasing surfactant concentration approximately fourfold from 14.1 ± 1.89 to 60.0 mg/kg in animal experiments was not associated with improved surfactant distribution in the lungs. Such data on large volume administration can be considered as a positive control validating the method used to analyze the surfactant distribution at a macroscopic level [11].

We hypothesized that the lower surfactant viscosity at low concentration would improve distribution, but also increase therapy effectiveness. To study this, we developed a study to assess an effect of reducing the concentration (viscosity) for the administered exogenous surfactant (poractant alfa) preparation without changing the recommended dose to determine most optimal strategy for surfactant replacement therapy by comparatively analyzing the results depending on the exogenous surfactant concentration/viscosity relation.

Aim: to assess an effect of PA administered at low (40 mg/mL) vs. standard (80 mg/mL) concentration without changing recommended dosage (200 mg/kg) on outcomes of preterm infants at gestational age (GA) under 32 weeks receiving various respiratory support.

Materials and Methods / Материалы и методы

Study design / Дизайн исследования

A prospective randomized controlled multicenter study was conducted. A total of 325 infants under 32 weeks of GA were randomized in the five perinatal centers. After randomization and birth, the infants received PA at a dose of 200 mg/kg at minute 10 of age if indicated.

Stabilization of patients in the delivery room was carried out according to a unified protocol. Infant condition was assessed immediately after PA administration and during the first hour of life as follows: presence of side effects and their severity after drug administration. Lung damage within 72 hours manifested as air leakage syndrome, pulmonary bleeding, and severe hemodynamic disorders. The third end point was to assess outcomes of patients at the time of discharge from the hospital or death. This study was conducted to investigate an effect of low surfactant concentration during surfactant replacement therapy on lung outcomes. Efficacy was defined as a combination of reducing a risk of lung damage and minimizing pulmonary and extrapulmonary complications of RDS in preterm infants.

Inclusion and exclusion criteria / Критерии включения и исключения

Inclusion criteria: 1) informed parental consent before enrollment into the trial; 2) preterm infants born at one of the five perinatal centers; 3) GA at the time of delivery at least 32 ⅐ (inclusive) weeks; 4) clinical need for respiratory therapy – non-invasive respiratory support or continuous positive airway pressure (CPAP), conventional mechanical ventilation (CMV), high frequency oscillatory ventilation (HFOV), oxygen therapy; 5) clinical indications for surfactant administration: for infants with birth weight of more than 1000 g – mean airway pressure (MAP) ≥ 7.0 cm H_2O and fraction of inspired oxygen (FiO_2) ≥ 0.4 to maintain the target oxygen saturation level of 90–94 %; for infants with birth weight less than 1000 g – MAP ≥ 7.0 cm H_2O and FiO_2 ≥ 0.3 to maintain the target oxygen level of 90–94 % in the absence of a pronounced respiratory activity (retracted compliant places of the thoracic cage above clavicles, suprasternal fossa and sternum); 6) exclusion of pneumothorax based on chest X-ray exam performed within the first two hours of life.

Exclusion criteria: 1) absence of informed parental consent before enrollment into the trial; 2) absence of indications for surfactant treatment; 3) chromosomal and genetic anomalies discovered antenatally or after birth; 4) congenital malformations, discovered antenatally or after birth, which might be involved in developing respiratory or cardiovascular insufficiency; 5) history of using various surfactant preparations during patient's treatment; 6) gross deviations from the research protocol.

As a result, from 325 preterm infants 61 subjects were excluded from the study for the following reasons: 28 children had no indications for surfactant administration at birth (in delivery room); 11 children had congenital malformations; two patients had birth injuries; two patients had acute renal failure and required peritoneal dialysis; one infant had hereditary metabolic disease (insufficiency of long-chain 3-hydroxyacyl-Co-A-fatty acid dehydrogenase – mutation NM_000182.4: c.1528G>C); 14 patients were excluded due to deviations from the study protocol, and in 3 cases the data were lost. The inclusion criteria were met by 264 children, which were randomized into study groups (**Fig. 2**).

Comparison groups / Группы сравнения

Parental consent was obtained, and randomization was performed in case of threat of the birth to a preterm infant with GA under 32 weeks. The patient randomiza-

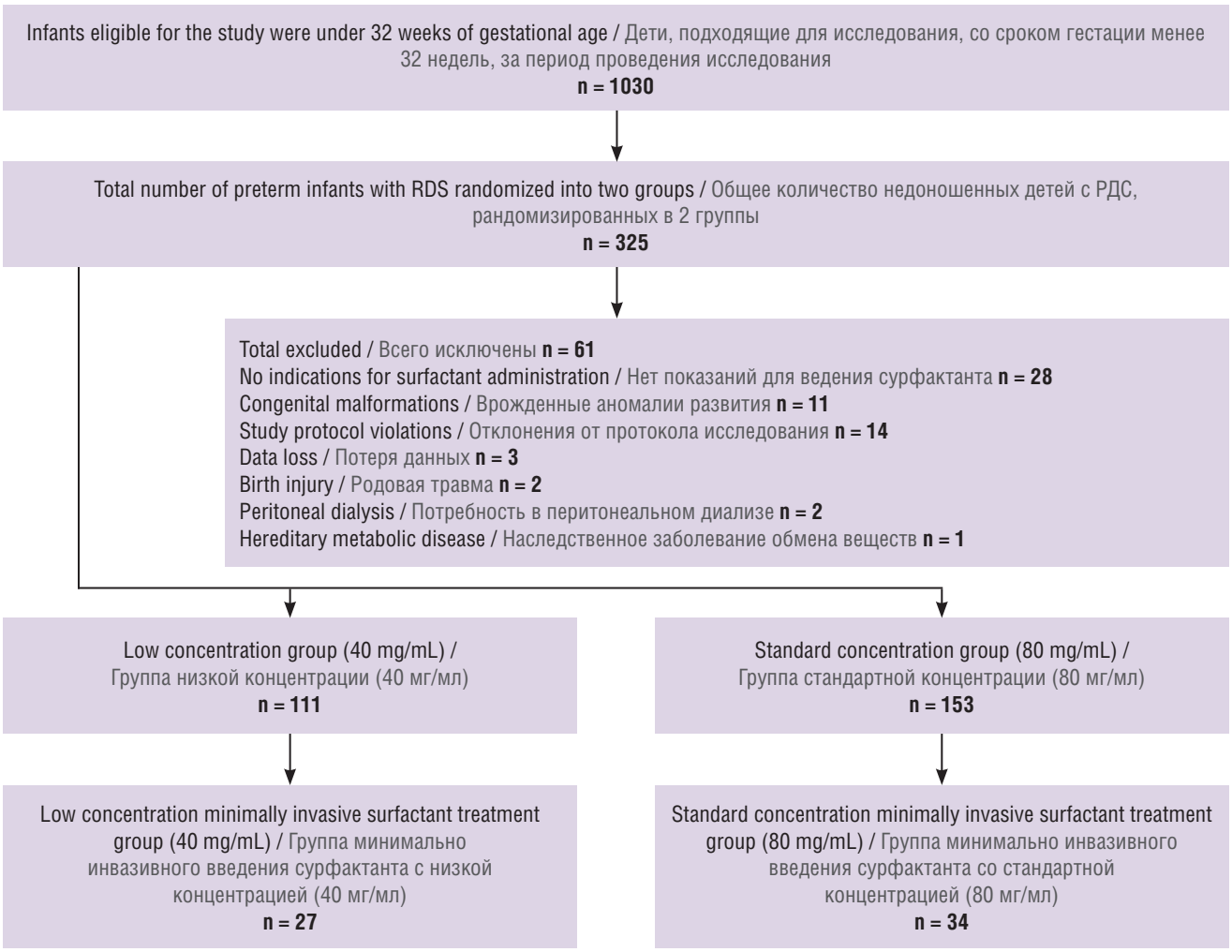

Figure 2. Patients included in the study (flowchart).
Note: *RDS – respiratory distress syndrome.*

Рисунок 2. Пациенты, включенные в исследование (блок-схема).
Примечание: *РДС – респираторный дистресс-синдром.*

tion was carried out by pulling closed envelopes immediately before delivery after obtaining informed consent by the parents. In the form of the envelope the number of patient medical history, patient's surname and doctor's surname, who performed randomization and surfactant administration, and depersonalized patient study identification number, which would subsequently be entered into the database, were recorded. The patient study identifiers were obtained by utilizing a random number generator and distributed among five perinatal centers. In case of medical indications for surfactant administration in the delivery room, a patient was included in the study. A minimally invasive method of surfactant administration was used in infants with spontaneous breathing. In case of no any indications for surfactant therapy, the envelope was drawn up in an identical manner and put in a separate folder.

Thus, two groups were formed and compared: Low concentration (LC) group – PA was administered in concentration 40 mg/mL (n = 111) and Standard concentration (SC) group (control) – PA was administered in concentration 80 mg/mL (n = 153). Additionally, we conducted a comparison in two subgroups with surfactant introduction by minimally invasive methods in spontaneously breathing infants (using LISA – a less invasive method of introducing surfactant through a thin catheter or endotracheal tube): subgroup LC – PA concentration was 40 mg/mL (n = 27) and subgroup SC (control) – PA concentration was 80 mg/mL (n = 34).

Study protocol / Протокол исследования

The study protocol assumed stabilization of the patients' condition using respiratory circuit with a T-piece connector and positive end expiratory pressure (PEEP) valve in delivery room. The minimal PEEP level was set within 6.0–8.0 cm H_2O, FiO_2 = 0.21–0.3 at the start. Blood oxygen saturation (SpO_2) was determined in the delivery room from birth using various monitors with Nellcor™

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pulse oximetry technology (MEDTRONIC, USA). Patient tracheal intubation and transfer to mechanical lung ventilation were performed to reach average MAP > 8.0 cm H_2O and FiO_2 > 0.4–0.5 to maintain the target SpO_2 level or absence of spontaneous respiration. At the age of 10 minutes of life, according to randomization data poractant alpha bolus was injected into the endotracheal tube (ETT) or using minimally invasive method of surfactant treatment (MIST), depending on infant's condition and capacity to breathe spontaneously. Before the end of stabilization in the delivery room, the following parameters were evaluated: cases of endotracheal tube obstruction, level of SpO_2 decline, the minimum SpO_2 value until recovery, cases of bradycardia and magnitude of maximum bradycardia before recovery. After stabilization, patients were transferred to the neonatal intensive care unit (NICU).

The next stage included assessment and observation of patients at the age of the first 72 hours of life. The following main parameters and events that could indicate severe lung damage during surfactant therapy were monitored: respiratory parameters (maximum FiO_2, MAP, tidal volume), the presence of air leak syndrome, pulmonary hemorrhage as a result of lung injury. The equipment for respiratory therapy (from different manufacturers) was available in perinatal centers. The main goal was to keep control of the tidal volume and maintain it at the minimal levels.

Study scheme is presented in **Figure 3**.

The outcomes were assessed based on the following indicators: 1) infant's condition immediately upon PA administration – signs of airways obstruction, bradycardia less than 100 beats per minute and its severity, decreased SpO_2 and intensity of SpO_2 decrease; 2) duration of invasive respiratory support; 3) overall duration of the respiratory therapy; 4) length of hospital stay; 5) the maximal values of following variables in the first 72 hours of life – MAP and FiO_2; 6) degree of manifested pulmonary injury (air leak syndrome, pulmonary hemorrhage); 7) neurological injuries – grade III intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL); 8) bronchopulmonary dysplasia (BPD), defined as a need for supplemental oxygen or respiratory support by 36 weeks of post-conception age; 9) necrotizing enterocolitis (NEC), surgical stage; 10) hemodynamically significant patent ductus arteriosus (HSPDA); 11) retinopathy of prematurity, surgical stage; 12) death (only the deaths in the first hospitalization period were included).

Ethical aspects / Этические аспекты

The study was conducted in accordance with the ethical standards of the 1964 Helsinki Declaration of the World Medical Association, its subsequent amendments and comparable ethical standards. The study was approved by the Ethics Committee of the Yaroslavl State Medical University, Protocol No. 45 dated of April 22, 2021.

Statistical analysis / Статистический анализ

Data collection was performed by researchers filling out a depersonalized electronic database in order of priority using Microsoft 365 spread sheets. Statistical analysis was carried out using the free Python computing software environment (v.3.8): built-in functions from the Statsmodels.api and Scipy modules for statistical calculations. Quantitative variables were evaluated for compliance with the normal distribution using the Shapiro–Wilk test. Aggregates of quantitative indicators, which distribution differed from normal were described using the median (Me) and the lower and upper quartiles ([Q_1; Q_3]). We used the Mann–Whitney U-test to compare unrelated

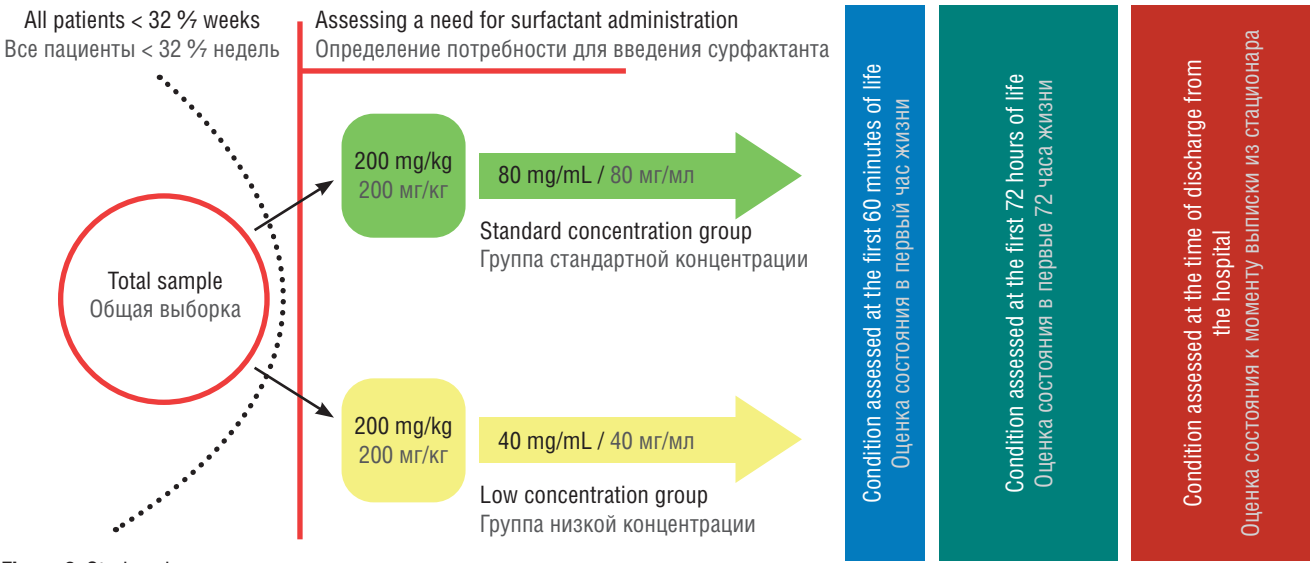

Figure 3. Study scheme.

Рисунок 3. Схема исследования.

samples. In the case of describing quantitative variables with normal distribution, the data obtained were combined into variational series in which arithmetic averages (M) and standard deviations (SD) were calculated. While comparing average values in normally distributed sets of quantitative data, the Student's t-test was calculated. The data of quantitative characteristics are expressed as absolute numbers and relevant proportions (%). The comparison of nominal group data was performed using the Pearson χ^2 test. In the case a number of expected observations in any of the cells in the four-field table was less than 10, Fisher's exact test was used to assess a significance level. A relationship of features was studied based on correlation analysis (Spearman test). The differences between values were considered statistically significant at $p \leq 0.05$.

Results / Результаты

Preparation of surfactant solution / Приготовление раствора сурфактанта

We used an exogenous surfactant – Curosurf® (poractant alfa licensed through Chiesi Farmaceutici, Parma, Italy). 153 preterm infants were included into SC group receiving PA at dose of 200 mg/kg, concentration 80 mg/mL. Indications for surfactant replacement therapy were in accordance with the 2016 clinical guidelines "Management of newborns with respiratory distress syndrome" at a dose of 200 mg/kg [12]. PA was supplied in ready-to-use, single-use vials containing 1.5 mL (120 mg phospholipid) of surfactant. Derived from minced porcine lung, PA is a creamy white, sterile suspension containing the surfactant in normal saline at a concentration of 80 mg/mL phospholipid. PA is prepared by chloroform-methanol extraction, and liquid-gel affinity chromatography, contains ~ 99 % polar lipids [13]. 111 preterm infants were included into LC group, who met the inclusion criteria and were given the first PA dose of 200 mg/kg (repeat dose 100 mg/kg), concentration of 40 mg/mL in the delivery room. The repeated surfactant administration was carried out in drug concentration given first time.

The surfactant was administered in a standardized manner: invasively (through the endotracheal tube in mechanically ventilated babies), minimally invasive in spontaneously breathing babies by LISA (Less Invasive Surfactant Administration) or using the INSURE strategy (INtubation–SURfactant – [immediate] Extubation). In our previous study with autopsy material, we measured trachea length in newborns with extremely low birth weight (ELBW) comprising 34.0 ± 5.0 mm from vocal cords to tracheal bifurcation [14]. Thus, we have determined the optimal depth of catheter insertion as 15–20 mm below the vocal cords. Surfactant injection by the LISA method was performed through a thin catheter (4–5 Fr) inserted under direct laryngoscopy control without using Magill forceps, along with non-invasive continuous maintenance of constant CPAP of at least 6.0 cm H_2O via mononasal tube or binasal cannulas using a device with a T-shaped connector [15]. The surfactant administration duration was 60–180 seconds controlled by attending neonatologist. The respiratory support strategy was determined by patient's clinical needs, because randomization was performed before infant's birth. In each group we analyzed the data based on mechanical lung ventilation and spontaneous ventilation. A separate analysis was carried out in the spontaneous ventilation subgroups of infants who received surfactant by the LISA and INSURE methods: subgroup LC (n = 27) – surfactant at a concentration of 40 mg/mL, subgroup SC (n = 34) – surfactant at a concentration of 80 mg/mL.

The diluted PA concentration was prepared dissolving surfactant preparation in 0.9 % sodium chloride solution at 1:1 ratio. For instance, to prepare poractant alfa 120 mg or 1.5 mL, there was added 1.5 mL of 0.9 % sodium chloride solution. Surfactant dilution with 0.9 % sodium chloride solution was performed directly in the syringe, by adding surfactant first followed by mixing. As a result, the total volume of a singular dose of 200 mg/kg was doubled in comparison to standard concentration.

Analysis of physical properties of surfactant preparations / Анализ физических свойств препаратов сурфактанта

PA drop at standard concentration and drop diluted two times with 0.9 % sodium chloride solution were placed on a glass slide from a height of 1.0 cm using a 1.0 mL syringe. The glass slide was pre-cleaned and degreased. The photo was taken under side illumination on a Nikon D750 camera with a Nikkor AF-S ED 18-300 mm VR lens with a focal length of 300 mm and a minimum distance to the object. The contact angles of wetting of surfactant solutions were measured using graphic computer software while processing photographs. Micrographs were taken with an iPhone 8 camera with adapter and a Nikon Eclipse Ci-S direct light microscope. The prepared standard and diluted surfactant drops were placed on a glass slide to take a photo 1.0 minute later at room temperature (**Fig. 4**).

Comparison of surfactant dynamic viscosity / Сравнение динамической вязкости сурфактантов

A dynamic viscosity of various surfactant samples was investigated. The study was carried out in the Laboratory of Biomedical Photonics, Faculty of Physics, Lomonosov Moscow State University. Surfactants rheological properties were studied using an RM100 CP1000 PLUS rotational viscometer (Lamy Rheology Instruments, France) with a CP40Z CERTIFIED cone-plate measuring system, at shear rates of 500, 1000, 1500, 2000 and 5000 s^{-1}. The viscosity study was carried out at a temperature of 22 °C (room temperature). Previously, surfactant dynamic viscosity was studied at various temperatures spanning

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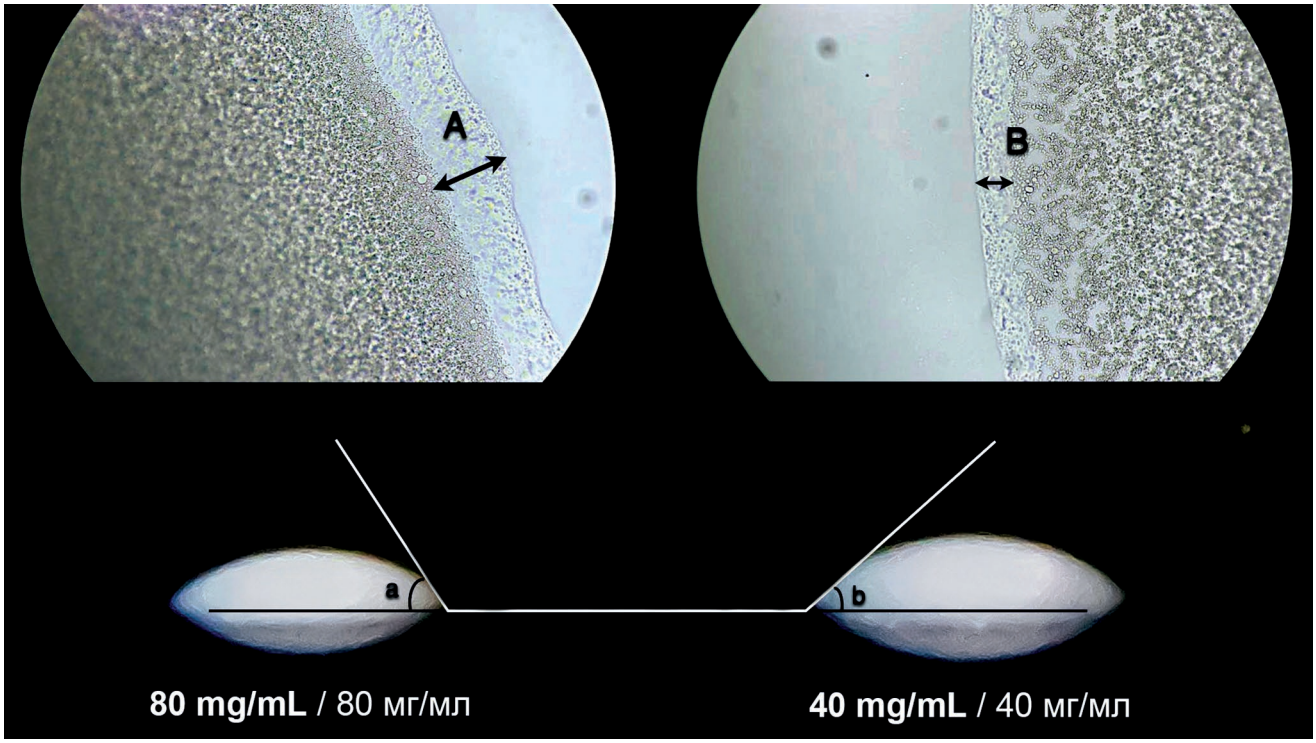

Figure 4. Formation of dry poractant alfa (PA) layer at standard concentration of 80 mg/mL (**A**) and low concentration of 40 mg/mL (**B**) for 1 minute on a glass slide (top panel, ×100). Spreading of PA drop at normal concentration (**a**) and diluted surfactant (**b**) and formation of an angle. Contact angles of wetting of surfactant solutions: angle a = 55°, angle b = 45°.

Рисунок 4. Верхний рисунок: образование сухого слоя порактанта альфа (ПА) в стандартной концентрации 80 мг/мл (**A**) и низкой концентрации 40 мг/мл (**B**) в течение 1 минуты на предметном стекле (×100). Нижний рисунок: растекание капли ПА нормальной концентрации и образование угла (**a**) и разбавленного сурфактанта и образование угла (**b**). Краевые углы смачивания растворами сурфактанта: угол a = 55°, угол b = 45°.

5, 22, 37 degrees Celsius finding no difference between temperature groups [16]. Therefore, in our experiment, we used solely solutions at room temperature (22 °C). When changing the sample, the measurement system was washed with distilled water followed by 95 % isopropyl alcohol; next, it was calibrated in height. The original PA solution with a phospholipid concentration of 80 mg/ml (Chiesi Farmaceutici, S.p.A., Parma, Italy) and PA solution diluted with 0.9 % sodium chloride solution at phospholipid concentration of 40 mg/mL as well as a beractant at phospholipid concentration of 25 mg were used as the object of the study 25 mg/mL (AbbVie Inc., North Chicago, USA). A 0.4 ml aliquot of each surfactant at room temperature was placed in the center of the sample dish using an insulin syringe. At the shear rates noted above, the viscosity reaches steady state within 10 seconds or more without markedly changed magnitude, so each measurement lasted a standard 60 seconds (viscosity was recorded at 60 seconds). For each determined shear rate, the experiment was repeated at least three times. Distilled water was used as the standard viscosity reference. The measured viscosity values for distilled water were within the error of 1 % and corresponded to the literature data [17].

Figure 4 shows the spreading effect of drops at standard (80 mg/mL) and reduced (40 mg/mL) PA concentration. In the latter, the angle between the diluted surfactant and the surface was much smaller.

In experimental work, the shear viscosity of Survanta, Curosurf and diluted Curosurf shows a wide range of values and dependence on shear rate at 22 °C (**Fig. 5**). Viscosity values for all surfactant mixtures increased with decreasing shear rate. Moreover, for the diluted Curosurf vs. other surfactants, the difference was the least significant.

The most significant changes in viscosity upon a tenfold increases shear rate from 500 to 5000 s^{-1} were found in beractant (constant temperature 22 °C) from 10.6 to 5.2 mPa×s. Viscosity decline was demonstrated for diluted PA of 2.0 to 1.5 mPa×s. Conventional PA showed no significant difference in viscosity upon shear rate ranged from 4.0 to 4.1 mPa×s. However, at all stages, the diluted PA showed half the viscosity or more compared to the conventional preparation, which may indicate in favor of greater fluidity.

Baseline clinical and anamnestic data of preterm infants / Основные клинико-анамнестические данные недоношенных детей

The analysis of baseline clinical and anamnestic data of preterm infants revealed no differences in all examined characteristics, excepting solely operative delivery

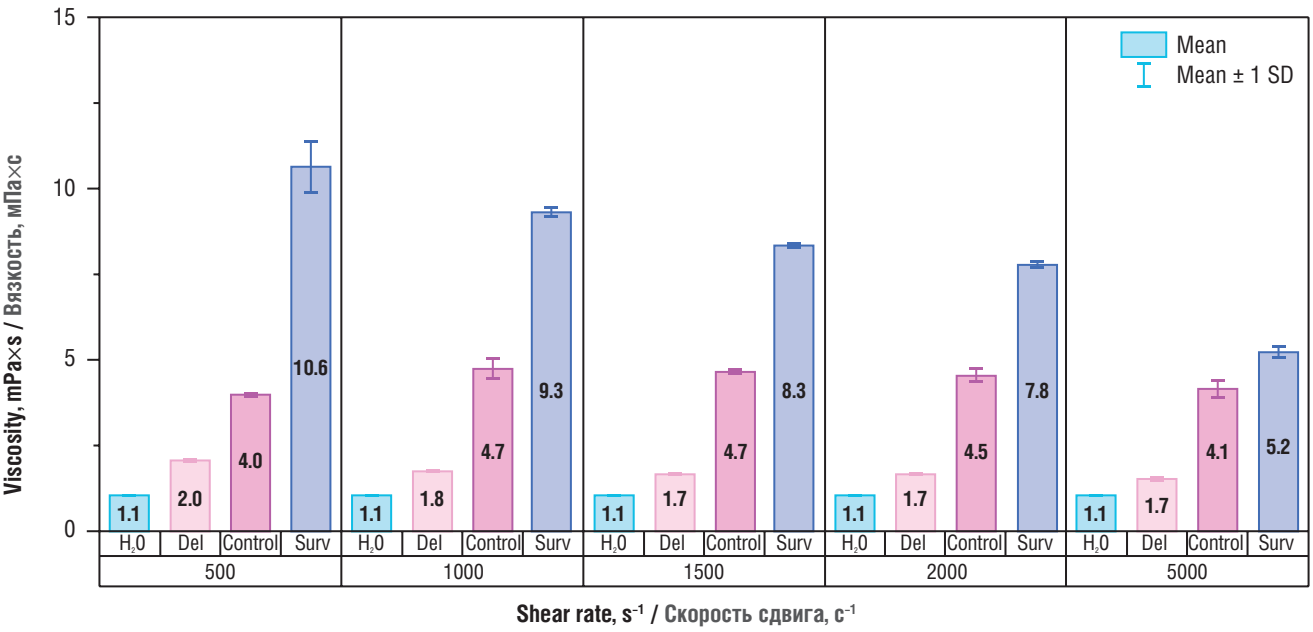

Figure 5. Surfactant viscosity at varying shear rates obtained during the experiment in the laboratory. H_20 – water used as reference in viscometer calibration; Del – twofold diluted poractant alfa (solution NaCl 0,9 %:poractant alfa = 1:1); Control – standard poractant alfa; Surv – beractant.

Рисунок 5. Вязкость сурфактантов при различных скоростях сдвига, полученная в ходе эксперимента в лаборатории. H_20 – вода, используемая в качестве эталона при калибровке вискозиметра; Del – двукратно разведенный порактант альфа (раствор NaCl 0,9 %:порактант альфа = 1:1); контроль – стандартный порактант альфа; Surv – беракант.

frequency, which in LC vs. SC group turned out to be significantly higher (**Table 1**).

The full course of steroid prophylaxis of RDS was carried out in 60–64 % of all cases in both groups. No differences in birth weight and GA at birth as well as Apgar score and gender distribution were found in both groups.

Surfactant use in preterm infants / Результаты применения сурфактанта у недоношенных детей

The first PA administration was performed applying different methods and, as a standard operating procedure, in the delivery room at the first 10 minutes of life (**Table 2**).

Table 1. Clinical characteristics of preterm infants.

Таблица 1. Клиническая характеристика недоношенных детей, вошедших в исследование.

Parameter Показатель	LC group Группа НК n = 111	SC group Группа СК n = 153	p value Значение p
Gestational age, weeks, Me [Q_1; Q_3] Гестационный возраст, недель, Me [Q_1; Q_3]	29.0 [26.5; 30.0]	28.0 [26.0; 30.0]	0.311
Birth weight, g, Me [Q_1; Q_3] Масса тела при рождении, г, Me [Q_1; Q_3]	1100.0 [865.0; 1400.0]	1060.0 [820.0; 1370.0]	0.285
Apgar score at minute 1, Me [Q_1; Q_3] Оценка по шкале Апгар на 1-й минуте, Me [Q_1; Q_3]	4.0 [4.0; 5.0]	5.0 [4.0; 5.0]	0.205
Apgar score at minute 5, Me [Q_1; Q_3] Оценка по шкале Апгар на 5-й минуте, Me [Q_1; Q_3]	6.0 [5.0; 7.0]	6.0 [5.0; 7.0]	0.149
Male, n (%) Мужской пол, n (%)	54 (48.6)	80 (52.3)	0.559
Full steroid course, n (%) Полный курс стероидов, n (%)	72 (64.9)	92 (60.1)	0.434
Cesarean section, n (%) Роды путем кесарева сечения, n (%)	85 (76.6)	100 (65.4)	0.049*

Note: *LC – low concentration; SC – standard concentration; * – significant differences according to χ^2 criterion.*

Примечание: *НК – низкая концентрация; СК – стандартная концентрация; * – различия статистически значимы по критерию χ^2.*

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Table 2. Methods of surfactant administration.

Таблица 2. Способы введения сурфактанта.

Parameter Показатель	LC group Группа НК n = 111	SC group Группа СК n = 153	p value Значение p
Age of life before first dose of surfactant, min, Me [Q_1; Q_3] Время жизни до введения первой дозы сурфактанта, мин, Me [Q_1; Q_3]	10.0 [8.0; 19.0]	10.0 [8.0; 20.0]	0.864
Surfactant administration through an endotracheal tube, n (%) Введение сурфактанта через эндотрахеальную трубку, n (%)	84 (75.7)	116 (75.8)	0.979
INSURE, n (%) Интубация-сурфактант-экстубация, n (%)	10 (9.0)	9 (5.9)	0.332
Less invasive surfactant administration, n (%) Менее инвазивное введение сурфактанта, n (%)	17 (15.3)	28 (18.3)	0.524

Note: *LC – low concentration; SC – standard concentration.*

Примечание: *НК – низкая концентрация; СК – стандартная концентрация.*

As shown from **Table 2**, in both groups, the invasive method of surfactant administration was prevalent, which was based on the severity of the condition of the children and by the presence of indication for tracheal intubation and subsequent invasive respiratory therapy in the delivery room. The least invasive PA administration in each of the groups was carried out to almost every fourth child who was also spontaneously breathing. At the same time, the analysis of the development of the signs of airway obstruction during the surfactant administration (bradycardia less than 100 beats per minute and its severity, a decrease in SpO_2 below 85 % and a minimum value of SpO_2 decrease) did not reveal any statistically significant differences between the groups of mechanically ventilated and spontaneously breathing babies (**Table 3**).

Table 3 shows the short-term effects of standard and diluted surfactant concentration during the first minutes after administration. No significant differences were found in both groups. The increase in volume of the administered surfactant also had no effect on the oxygen demand as well as MAP and tidal volumes at the first 72 hours of life (**Table 4**).

The level requiring CMV and/or HFOV repeated surfactant administrations as well as duration of invasive respiratory support are presented in **Table 5**.

As shown in **Table 5**, the vast majority of children in both groups required invasive respiratory therapy, whereas every 4^{th}–5^{th} child required HFOV use. The need for repeated surfactant administration and the age of repeated administration did not differ between

Table 3. Development of bradycardia and the decrease in blood oxygen saturation during surfactant administration to preterm infants with respiratory distress syndrome.

Таблица 3. Развитие брадикардии и снижение сатурации крови кислородом при введении сурфактанта недоношенным детям с респираторным дистресс-синдромом.

Parameter Показатель	LC group Группа НК n = 111	SC group Группа СК n = 153	p value Значение p
Bradycardia incidence upon surfactant administration, n (%) Частота встречаемости брадикардии на фоне введения сурфактанта, n (%)	10 (9.0)	12 (7.8)	0.735
Minimal heart rate values during surfactant administration, beats per minute, Me [Q_1; Q_3] Минимальные значения частоты сердечных сокращений при введении сурфактанта, ударов в мин, Me [Q_1; Q_3]	89.0 [80.5; 93.7]	93.0 [81.0; 98.0]	0.254
The drop of blood oxygen saturation incidence upon surfactant administration, n (%) Снижение уровня насыщения крови кислородом при введении сурфактанта, n (%)	61 (55.0)	77 (50.0)	0.457
Minimal blood oxygen saturation values during surfactant administration, %, Me [Q_1; Q_3] Минимальные значения насыщения крови кислородом при введении сурфактанта, %, Me [Q_1; Q_3]	78.0 [70.0; 83.0]	78.5 [72.0; 82.0]	0.454

Note: *LC – low concentration; SC – standard concentration.*

Примечание: *НК – низкая концентрация; СК – стандартная концентрация.*

Table 4. Maximal parameters of the invasive respiratory therapy for examined children in the first 72 hours of life.

Таблица 4. Максимальные параметры инвазивной респираторной терапии обследованных детей в первые 72 часа жизни.

Parameter Показатель	LC group Группа НК n = 111	SC group Группа СК n = 153	p value Значение p
Maximal FiO_2, Me [Q_1; Q_3] Максимальная FiO_2, Me [Q_1; Q_3]	0.3 [0.3; 0.45]	0.3 [0.3; 0.45]	0.487
Maximal MAP, cm H_2O, Me [Q_1; Q_3] Максимальное МАР, см вод. ст, Me [Q_1; Q_3]	9.0 [8.0; 10.0]	9.1 [8.0; 10.0]	0.395
Maximal tidal volume, mL, Me [Q_1; Q_3] Максимальный дыхательный объем, мл, Me [Q_1; Q_3]	5.0 [5.0; 5.5] n = 54	5.0 [5.0; 5.0] n = 53	0.283

Note: *FiO_2 – fraction of inspiratory oxygen; MAP – mean airway pressure; LC – low concentration; SC – standard concentration.*

Примечание: *FiO_2 – фракция вдыхаемого кислорода; МАР – среднее давление в дыхательных путях; НК – низкая концентрация; СК – стандартная концентрация.*

Table 5. Respiratory outcomes of the children examined.

Таблица 5. Респираторные исходы обследованных детей.

Parameter Показатель	LC group Группа НК n = 111	SC group Группа СК n = 153	p value Значение p
Required CMV, n (%) Потребность в ИВЛ, n (%)	91 (82.0)	127 (83.0)	0.829
Required HFOV, n (%) Потребность в ВЧО ИВЛ, n (%)	23 (21.3)	36 (26.1)	0.383
Required repeated surfactant administration, n (%) Необходимость повторного введения сурфактанта, n (%)	26 (23.4)	27 (17.6)	0.247
Age of life before repeated surfactant administration, hours, M ± SD Время жизни до повторного введения сурфактанта, ч, M ± SD	6.6 ± 1.0	7.1 ± 1.5	0.728
Duration of total respiratory support, hours, Me [Q_1; Q_3] Продолжительность тотальной респираторной поддержки, ч, Me [Q_1; Q_3]	375.0 [141.5; 1049.0]	470.0 [175.0; 1055.0]	0.197

Note: *CMV – conventional mechanical ventilation; HFOV – high frequency oscillatory ventilation; LC – low concentration; SC – standard concentration.*

Примечание: *ИВЛ – искусственная вентиляция легких; ВЧО ИВЛ – высокочастотная осцилляторная искусственная вентиляция легких; НК – низкая концентрация; СК – стандартная концентрация.*

the groups with different surfactant concentration and volume.

To avoid potential effect of a congenital infection on the study data, we comparatively analyzed inflammation markers in preterm children at the first 72 hours of life (**Table 6**).

Table 6 shows the markers of inflammation primarily C-reactive protein (CRP) finding no significant differences between the LC and SC groups ($p \geq 0.05$). However, it tended to decrease based on the approach assuming that infectious markers are more pronounced in the LC group. Apparently, the number of infants with thrombocytopenia was significantly higher in the group with the surfactant concentration of 40 mg/mL allowing to consider it as a risk factor of increased hemorrhagic complications. However, according to the data presented in **Table 7**, pulmonary hemorrhages developed at significantly higher level after receiving surfactant at concentration of 80 mg/mL.

In order to assess a relationship between pulmonary hemorrhage and other clinical and laboratory characteristics, we performed a statistical analysis using Spearman's rank correlation coefficient that uncovered a direct correlation between pulmonary hemorrhage and HSPDA ($r = 0.318$; $p < 0.001$). Not only did pulmonary hemorrhage prolongs the length of stay in the NICU ($r = 0.488$; $p < 0.001$), but it also increased a risk of death ($r = 0.507$; $p < 0.001$). At the same time, the incidence of IVH grade III, PVL, BPD, pneumothorax and lethal outcomes was comparable in both groups.

An analysis of the clinical data from spontaneously breathing preterm infants in LC and SC subgroups demonstrated no significant inter-group differences for all signs presented in **Table 8**, which allowed the comparison of the discussed subgroups.

The response to surfactant administration and outcomes in both subgroups are presented in **Table 9**.

Comparing the two subgroups from all spontaneously breathing patients in our study who received noninvasive respiratory support we obtained a significant difference in ventilatory support duration and BPD development: 142.0 [70.0; 219.0] hours vs. 250.5 [141.0; 690.0] hours ($p = 0.008$) and 1 (4.0 %) vs. 10 (29 %) ($p = 0.009$) respectively.

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Table 6. Inflammation markers at the first 72 hours of life in preterm infants with respiratory distress syndrome.

Таблица 6. Маркеры воспаления в первые 72 часа жизни у недоношенных детей с респираторным дистресс-синдромом.

Parameter Показатель	LC group Группа НК n = 111	SC group Группа СК n = 153	p value Значение p
Infants with leukopenia (< 5.0×10^9/L), n (%) Младенцы с лейкопенией (< $5,0\times10^9$/л), n (%)	18 (16.2)	22 (14.4)	0.681
Infants with leukocytosis (> 30.0×10^9/L), n (%) Младенцы с лейкоцитозом (> $30,0\times10^9$/л), n (%)	15 (13.5)	28 (18.3)	0.298
Infants with neutrophilic index > 0.2, n (%) Младенцы с нейтрофильным индексом > 0,2, n (%)	34 (30.6)	36 (23.5)	0.197
Infants with CRP > 6 mg/L, n (%) Младенцы с уровнем СРБ > 6 мг/л, n, (%)	39 (35.1)	37 (24.2)	0.052
Infants with thrombocytopenia (< 150×10^9/L), n (%) Младенцы с тромбоцитопенией (< 150×10^9/л), n (%)	48 (43.2)	38 (24.8)	0.002*

Note: *CRP – C-reactive protein; LC – low concentration; SC – standard cconcentration; * – significant differences according to χ^2 criterion.*

Примечание: *СРБ – С-реактивный белок; НК – низкая концентрация; СК – стандартная концентрация; * – различия статистически значимы по критерию χ^2.*

Table 7. Outcomes of nursing of preterm infants with respiratory distress syndrome.

Таблица 7. Исходы у обследованных недоношенных детей с респираторным дистресс-синдромом.

Parameter Показатель	LC group Группа НК n = 111	SC group Группа СК n = 153	p value Значение p
Surgical stage of necrotizing enterocolitis, n (%) Хирургическая стадия некротического энтероколита, n (%)	3 (2.7)	5 (3.3)	0.791
Bronchopulmonary dysplasia, n (%) Бронхолегочная дисплазия, n (%)	39 (35.1)	60 (39.2)	0.499
Intraventricular hemorrhage grade III, n (%) Внутрижелудочковое кровоизлияние III степени, n (%)	18 (16.2)	21 (13.7)	0.601
Pneumothorax, n (%) Пневмоторакс, n (%)	1 (0.9)	5 (3.3)	0.200
Retinopathy of prematurity, surgical stage, n (%) Ретинопатия недоношенных, хирургическая стадия, n (%)	11 (9.9)	8 (5.2)	0.1387
Periventricular leukomalacia, n (%) Перивентрикулярная лейкомаляция, n (%)	5 (4.5)	13 (8.6)	0.206
Hemodynamically significant ductus arteriosus, n (%) Гемодинамически значимый артериальный проток, n (%)	19 (17.1)	25 (16.3)	0.867
Pulmonary hemorrhage, n (%) Легочное кровотечение, n (%)	4 (3.6)	20 (13.1)	0.008*
Lethal outcomes, n (%) Летальные исходы, n (%)	6 (5.4)	14 (9.2)	0.347

Note: *LC – low concentration; SC – standard concentration; * – significant differences according to χ^2 criterion.*

Примечание: *НК – низкая концентрация; СК – стандартная концентрация; * – различия статистически значимы по критерию χ^2.*

In the two subgroups with surfactant treatment without mechanical lung ventilation there were revealed significant differences in outcomes depending on PA concentration. In patients with PA concentration of 40 mg/mL, the total duration of respiratory support was significantly shorter, while the incidence of BPD was significantly lower, which probably influenced overall duration of hospitalization both in the NICU and in the hospital, because it was significantly shorter in the LC subgroup. No difference in the bradycardia incidence and drop-in blood oxygen saturation in response to surfactant were found between the groups, i. e., an increase in PA volume did not lead to a reduced tolerance.

Discussion / Обсуждение

We studied the effects on respiratory support, (serious) adverse events and short-term outcomes in two groups of preterm infants after receiving similar total surfactant dose but split into varying concentrations and thus different volumes. Surfactant volume was doubled while lowering the concentration by 50 %. We did not

Table 8. Subgroup clinical characteristics of preterm infants with spontaneous breathing.

Таблица 8. Клиническая характеристика недоношенных новорожденных в подгруппах со спонтанным дыханием.

Parameter Показатель	Subgroup LC Подгруппа НК n = 27	Subgroup SC Подгруппа СК n = 34	p value Значение p
Gestational age, weeks, Me [Q_1; Q_3] Гестационный возраст, недель, Me [Q_1; Q_3]	30.0 [29.0; 31.0]	29.5 [27.0; 30.0]	0.063
Birth weight, g, Me [Q_1; Q_3] Масса тела при рождении, г, Me [Q_1; Q_3]	1300.0 [1040.0; 1517.5]	1245.0 [983.75; 1452.5]	0.198
Apgar score at minute 1, Me [Q_1; Q_3] Оценка по шкале Апгар на 1-й минуте, Me [Q_1; Q_3]	6.0 [6.0; 6.0]	6.0 [5.0; 6.0]	0.058
Apgar score at minute 5, Me [Q_1; Q_3] Оценка по шкале Апгар на 5-й минуте, Me [Q_1; Q_3]	7.0 [7.0; 7.0]	7.0 [7.0; 7.0]	0.133
Male, n (%) Мужской пол, n (%)	14 (52.0)	22 (65.0)	0.311
Full steroid course, n (%) Полный курс стероидов, n (%)	19 (70.0)	23 (68.0)	0.074
Cesarean section, n (%) Кесарево сечение, n (%)	21 (78.0)	19 (56.0)	0.407

Note: *LC – low concentration; SC – standard concentration.*

Примечание: *НК – низкая концентрация; СК – стандартная концентрация.*

Table 9. Response to surfactant administration and main outcomes in preterm infants with minimally invasive surfactant administration at varying drug concentrations.

Таблица 9. Ответ на введение сурфактанта и основные исходы у недоношенных детей при минимально инвазивном введении сурфактанта в различных концентрациях.

Parameter Показатель	Subgroup LC Подгруппа НК n = 27	Subgroup SC Подгруппа СК n = 34	p value Значение p
Bradycardia incidence upon surfactant administration, n (%) Частота встречаемости брадикардии на фоне введения сурфактанта, n (%)	4 (15.0)	6 (18.0)	0.457
Declined blood oxygen saturation incidence upon surfactant administration, n (%) Падение сатурации крови кислородом при введении сурфактанта, n (%)	15 (56.0)	17 (50.0)	0.667
Duration of total respiratory support, hours, Me [Q_1; Q_3] Продолжительность общей респираторной поддержки, ч, Me [Q_1; Q_3]	142.0 [70.0; 219.0]	250.5 [141.0; 690.0]	0.008*
Bronchopulmonary dysplasia, n (%) Бронхолегочная дисплазия, n (%)	1 (4.0)	10 (29.0)	0.009*
Pulmonary hemorrhage, n (%) Легочное кровотечение, n (%)	0 (0.0)	1 (3.0)	0.369
Lengths of stay in intensive care unit, days, Me [Q_1; Q_3] Длительность пребывания в отделении реанимации и интенсивной терапии, дней, Me [Q_1; Q_3]	8.0 [7.5; 13.0]	14.0 [8.0; 33.75]	0.014*
Length of hospital stay, days, Me [Q_1; Q_3] Общая продолжительность госпитализации в стационаре, дни, Me [Q_1; Q_3]	38.0 [26.5; 48.5]	50.5 [36.25; 62.5]	0.014*

Note: *LC – low concentration; SC – standard concentration; * – significant differences according to χ^2 criterion.*

Примечание: *НК – низкая концентрация; СК – стандартная концентрация; * – различия статистически значимы по критерию χ^2.*

encounter technical problems in administering the larger volume, even to spontaneously breathing babies. We did not find a negative effect of diluted surfactant on outcomes in preterm infants with GA under 32 weeks. Moreover, a significantly increased risk of developing pulmonary hemorrhage was found in the case of surfactant used at concentration of 80 mg/mL (SC group) vs. LC group.

Each drug treatment depends on the five essential questions of what drug at which dose at which time to which patient via which route. Surfactant replacement therapy was the first therapy deliberately developed for preterm babies. The introduction of the surfactant replacement therapy is an example of how dose and timing were prospectively tested [1]. We were however unable

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to find publications comparing the effect of different surfactant concentrations within same total dose on infants' outcomes. We now studied a reduced surfactant concentration. The decrease in concentration was achieved by increasing the surfactant volume however maintaining the dose. The results of our study demonstrated that there was no increase in unfavorable outcome incidence regarding the volume of surfactant administered when it was doubled. To our knowledge, this is the first study to prospectively compare the same surfactant dose given with different concentrations in preterm babies.

We found a decline in pulmonary hemorrhages in mechanically ventilated babies treated with a lower concentration. The increased risk of pulmonary hemorrhage with patent HSPDA has been described in numerous studies [19–21]. We noted no HSPDA difference between the groups. Pulmonary hemorrhages could have been triggered by congenital infectious processes, however no significant differences between such risk factors in the groups were found. Moreover, the LC group tended to have a higher incidence of CRP concentrations exceeding 6.0 mg/L, therefore we suspect more congenital infectious processes, which could predispose, among other things considered, to developing pulmonary hemorrhage. Thus, we have no obvious explanation for the increased frequency of pulmonary hemorrhages in our study other than the difference in effect of PA doses 80 mg/mL vs. 40 mg/mL. We speculate that perhaps the more viscous surfactant, being distributed less evenly in the lungs, contributed to a more mosaic distribution in the lungs, their opening and the involvement of the alveoli in the gas exchange process. This perfusion-ventilation mismatch can lead to a higher risk of lung tissue damage in the most extended and possibly even compensatory over-inflated areas.

In our study HSPDA incidence in preterm infants with GA under 32 weeks did not exceed that in other studies. Thus, S. Ngo et al. (2017) [22] showed that the 2014 incidence of patent ductus arteriosus (PDA) in 134 hospitals in California (USA) was 38.5 %, whereas only 15.7 % cases required pharmacological treatment, which is comparable with our data – 16.3–17.1 %, respectively. In another observational study, J.I. Hagadorn et al. (2016) showed that over a 10-year period there were recorded 42 % of patients weighing less than 1500 g with PDA, of whom 74 % required pharmacological or surgical treatment [23]. The same was found with the incidence of IVH grade III (ICD-10 – P52.2), which is comparable with the data by P. Härkin et al. (2021) [25] for infants with GA under 28 weeks and is 15.7 % (in our study 13.7–16.2%) as well as in study by X. Kong et al. (2016) for patients up to 31 full weeks – 15.4% [25]. BPD incidence when defined as the need for oxygen and/or respiratory support by 36 weeks of post-conceptual age in our study is virtually equal to BPD incidence presented in the review by D. Hines et al. (2017), and ranges from 15 to 55 % (in our study – 35.1–39.2 %) [26].

Another cause of pulmonary hemorrhage may be the plug formation in the airways occurring when externally instilled liquid obstruction form and are transported through the flexible airway networks. Plug propagation in airway branches, distribution in the lung, and resulting wall stresses may affect therapeutic efficiency and even cause additional lung injury [27]. It is thus of great importance to study the mechanisms of liquid plug propagation in theory and practice. This will be a challenge because a 2021 neonatologist's survey in the Russian Federation described that most of them were afraid to use «large» surfactant volumes in ELBW patients [28].

The use of less invasive respiratory support methods in our study reduced BPD risk by 50 %. However, it was a surprise for us that this low PA concentration (40 mg/mL) significantly reduced BPD incidence in preterm infants with GA under 32 weeks in case PA was administered in a minimally invasive manner. Perhaps, in our study, this is due to a decrease in the duration of respiratory support allowing to reduce a risk of lung damage during respiratory therapy. As a result, such an improvement led to a faster discharge from hospital. Unfortunately, it is not possible to compare these findings with other similar clinical studies.

Considering the positive effect of a diluted surfactant, we can highlight several directions for studying this phenomenon. First, a change in surfactant physical properties (viscosity, fluidity) can contribute to a more even drug distribution in large-caliber bronchi, as well as in small bronchioles (Marangoni effect) due to a less prominent properties of a non-Newtonian fluid under gravity conditions. Secondly, the reduced surfactant concentration may promote better spreading, which leads to a more even distribution. The low viscosity in the diluted surfactant contributed to a greater drug penetration into the small airways and better filling of the bronchioles. The increased aliquot volume also helps to ensure good surfactant distribution.

Third, D. Luca et al. (2014) recommended adding 10–15 % to the required surfactant dose due to the inevitable reflux-related surfactant loss during minimally invasive administration [29]. In our study, we did not change the dose and kept it at 200 mg/kg. If there was a recommendation or need to increase a dose due to preparation losses, then dilution would allow to moderately compensate for it.

Summarizing, low PA concentration at 40 mg/mL in a total dose of 200 mg/kg did not negatively affect the outcome results in preterm infants with GA under 32 weeks. A twofold increase in administered PA volume did not affect PA tolerance, did not increase a risk of developing hypoxemia and bradycardia and relevant severity immediately upon drug administration, and did not aggravate respiratory and neurological outcomes. Moreover, minimally invasive administration of a surfactant with a PA concentration of 40 mg/mL reduced the risk of BPD probably also lowering a need for respiratory therapy.

Poractant alfa at a concentration of 80 mg/mL may predispose to an increased risk of pulmonary hemorrhage during mechanical lung ventilation.

Conclusion / Заключение

PA use at a concentration of 40 mg/mL without changing the recommended dose did not aggravate nursing preterm infants with GA under 32 weeks. With minimally invasive PA administration at concentration of 40 mg/mL, risk of bronchopulmonary dysplasia decreased, and when used in infants on mechanical lung ventilation, it lowered a risk of pulmonary hemorrhage. Hence, the findings discussed require to further conduct large prospective, multicenter, randomized studies enrolling large patient cohorts.

ARTICLE INFORMATION	ИНФОРМАЦИЯ О СТАТЬЕ
Received: 19.09.2023. **Revision received:** 18.10.2023.	**Поступила:** 19.09.2023. **В доработанном виде:** 18.10.2023.
Accepted: 20.10.2023. **Published online:** 20.10.2023.	**Принята к печати:** 20.10.2023. **Опубликована онлайн:** 20.10.2023.
Author's contribution	**Вклад авторов**
All authors participated equally in the collection, analysis and interpretation of the data.	Все авторы принимали равное участие в сборе, анализе и интерпретации данных.
All authors have read and approved the final version of the manuscript.	Все авторы прочитали и утвердили окончательный вариант рукописи.
Conflict of interests	**Конфликт интересов**
The authors declare no conflict of interests.	Авторы заявляют об отсутствии конфликта интересов.
Funding	**Финансирование**
The authors declare no funding.	Авторы заявляют об отсутствии финансовой поддержки.
Restrictions	**Ограничения**
One of the limitations of our work is the lack of stratification of patients by body weight into very low and extremely low birth weight; a detailed analysis of pediatric morbidity was not carried out. Small number of patients in the minimally invasive surfactant group. Altogether, and potentially other features, must be taken into account while planning new, prospective studies.	Одним из ограничений нашей работы является отсутствие стратификации пациентов по весовым группам на очень низкую и экстремально низкую массу тела при рождении, не проводился детальный анализ заболеваемости детей. Малая численность пациентов в группе малоинвазивного сурфактанта. Все эти и, возможно, ряд других особенностей предстоит учесть при планировании новых, проспективных исследований в будущем.
Acknowledgements	**Благодарности**
The authors express gratitude to the director of statistics of LLC "Techdepartament", Department Statistics for Medicine", PhD, E.V. Shchepkina for statistical data processing. We warmly thank for the help in collecting the material the doctors at all perinatal centers and personally Nailya Kharitonova, Olga Avdei, Marina Kovaleva, Anastasia Petrova, Maksim Kondrat'ev, Inessa Mebelova, Maksim Tkachuk, Olga Sapun for organizing work in locations. Special thanks to Petr Ermolinsky, Laboratory of Biomedical Photonics, Faculty of Physics, Lomonosov Moscow State University, and Leonid Karpov (student at the International Faculty of Pirogov Russian National Research Medical University) for help in preparing the study. The authors express deep gratitude to Dr Sci Med Boris Kramer, Chief Scientific Officer, Chief Medical Director of Neuroplast BV (Maastricht, the Netherlands), Clinical Professor University of Western Australia, for scientific advice in preparing the manuscript for publication and highly assessed quality of our study.	Авторы выражают благодарность директору по статистике ООО «Техдепартамент», отдел статистики медицины, к.с.н. Е.В. Щепкиной за статистическую обработку данных. Сердечно благодарим за помощь в сборе материала врачей всех перинатальных центров и лично Наилю Харитонову, Ольгу Авдей, Марину Ковалёву, Анастасию Петрову, Максима Кондратьева, Инессу Мебелову, Максима Ткачука, Ольгу Сапун за организацию работы на локациях. Также благодарим Петра Ермолинского из лаборатории биомедицинской фотоники физического факультета МГУ им. М.В. Ломоносова и Леонида Карпова (студента международного факультета ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России) за помощь в подготовке исследования. Авторы выражают особую глубокую благодарность доктору Борису Крамеру, д.м.н., главному научному сотруднику, главному медицинскому директору Neuroplast BV (Маастрихт, Нидерланды), клиническому профессору Университета Западной Австралии, за научные консультации при подготовке материала к публикации и за его высокую оценку качества нашего исследования.
Patient consent	**Согласие пациентов**
Obtained.	Получено.
Ethics approval	**Одобрение этического комитета**
The study was approved by the Ethics Committee of Yaroslavl State Medical University, Protocol No. 45, dated of April 22, 2021.	Исследование одобрено этическим комитетом ФГБОУ ВО ЯГМУ Минздрава России, протокол № 45 от 22.04.2021.
Clinical Trials Disclosure Policy	**Политика раскрытия данных**
The study protocol, statistical analysis plan, analysis principles, individual participant data underlying the results presented in this article after de-identification, 9 months and up to 3 years after the publication of the article will be available to investigators whose intended use of the data was approved by the designated purpose by an independent review committee ("trained facilitator"), for meta-analysis of individual participant data. Offers should be sent to the mailbox alvalmost@gmail.com. To gain access, data requesters will be required to sign a data access agreement.	Протокол исследования, план статистического анализа, принципы анализа, данные об отдельных участниках, лежащие в основе результатов, представленных в этой статье после деидентификации, спустя 9 месяцев и до 3 лет после публикации статьи будут доступны исследователям, чье предполагаемое использование данных было одобрено назначенным для этой цели независимым комитетом по рассмотрению («обученный посредник»), для метаанализа данных индивидуальных участников. Предложения должны быть направлены на почтовый ящик alvalmost@gmail.com. Чтобы получить доступ, лица, запрашивающие данные, должны будут подписать соглашение о доступе к данным.
Provenance and peer review	**Происхождение статьи и рецензирование**
Not commissioned; externally peer reviewed.	Журнал не заказывал статью; внешнее рецензирование.

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Obstetrics, Gynecology and Reproduction

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