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Significance of surfactant proteins in respiratory distress syndrome in preterm infants

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Respiratory diseases are considered to be widespread pathologies among preterm infants.
The research **aim** was to determine the level of surfactant protein A (SP-A) in the blood and tracheobronchial lavage of infants with respiratory distress syndrome (RDS) and pneumonia, as well as to study its significance in predicting pathological processes in the lungs.
Materials and methods. The study involved 80 very low birth weight infants with respiratory distress (2a — subgroup RDS, 2b — pneumonia), 42 extremely low birth weight infants (3a — RDS and 3b — pneumonia subgroups), and 20 children without respiratory distress (control group — 1).
Results. The initial examination showed that the level of SP-A in venous blood in the control group was 2.9±2.3 ng/ml, while in the 2b group, it was 21.2 ng/ml, which was 7.1 times higher compared to the control group. In group 2, the difference between 2b (21.2 ng/ml) and 2a (6.01 ng/ml) was determined to be 3.5 times. A direct correlation was observed between the level of SP-A in the blood and the oxygen dependence of patients with RDS ($r=0.240$, $p<0.05$). In addition, an increase in the level of the inflammatory marker C-reactive protein (CRP) was observed in these patients over time, and a correlation was found between the level of SP-A in the blood and CRP. When comparing the level of SP-A between deceased and surviving infants, it was found to be that SP-A 2.9 times higher in the blood of deceased patients compared to surviving infants, and conversely, 2.3 times higher in tracheobronchial lavage in surviving infants compared to the deceased patients. Based on the results obtained, the importance of SP-A in the differential diagnosis and prognosis of RDS is emphasized.
The research was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the institution indicated in the work. The informed consent of the children's parents was obtained for conducting the studies.
No conflict of interests was declared by the authors.
Keywords: newborns, respiratory distress syndrome, pneumonia, immune status, surfactant protein A, preterm infants.

Значення білків сурфактанта за респіраторного дистрес-синдрому в недоношених дітей

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Захворювання органів дихання є широко розповсюдженою патологією серед недоношених дітей.
Метою дослідження було визначення рівня сурфактантного білка А (SP-A) у крові та трахеобронхіальному лаважі дітей раннього віку з респіраторним дистрес-синдромом (РДС) і пневмонією, а також вивчення його значення у прогнозуванні патологічних процесів у легенях.
Матеріали і методи. У дослідженні взяло участь 80 дітей із дуже низькою масою тіла при народженні з респіраторним дистресом (2а — підгрупа РДС, 2б — пневмонія), 42 дитини з екстремально низькою масою тіла при народженні (підгрупи 3а — РДС, 3b — пневмонія) і 20 дітей без дихальної недостатності (контрольна група).
Результати. Під час первинного обстеження виявлено, що рівень SP-A у венозній крові в контрольній групі становив 2,9±2,3 нг/мл, а у групі 2б — 21,2 нг/мл, що було в 7,1 раза вище, ніж у контрольній групі. У групі 2 різниця між 2b (21,2 нг/мл) та 2а (6,01 нг/мл) — 3,5 раза. Простежено пряму кореляцію між рівнем SP-A у крові та кисневою залежністю хворих із РДС. Крім того, в цих хворих згодом спостерігалось підвищення рівня маркера запалення С-реактивного білка (СРБ), а також виявлено взаємозв'язок між рівнем SP-A у крові та СРБ. Зіставлення рівня SP-A в померлих малюків і тих, які вижили, виявило, що SP-A у крові померлих хворих у 2,9 раза вище, і навпаки, у трахеобронхіальному лаважі у 2,3 рази вище у тих, які вижили, порівняно з померлими. На підставі отриманих результатів підкреслюється значення SP-A в диференційній діагностиці та прогнозі РДС.
Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду батьків дітей.
Автори заявляють про відсутність конфлікту інтересів.
Ключові слова: новонароджені, респіраторний дистрес-синдром, пневмонія, імунний статус, сурфактантний білок А, недоношені діти.

Introduction

Preterm birth is considered to be a significant medical and social health issue worldwide, not only due to high mortality rates, but also because future disabilities for infants in this group are often associated with high medical costs.

According to the World Health Organization (WHO), 15 million babies are born prematurely every year, accounting for 10% of all newborns [6].

Among the pathological conditions in preterm infants, respiratory distress occupies a special place, attributed to the immaturity of the respiratory system associated with preterm birth [8]. The underdevelopment of the lungs and immune system in preterm infants is considered to be a significant risk factor for increased morbidity and mortality rates [3].

The main reason is associated with changes in the quantity and quality of surfactant synthesized by type II alveolar cells in the lungs. The primary physiological function of surfactant is to reduce alveolar surface tension and regulate gas exchange. Human surfactant consists of 80–85% lipids, 8–9% proteins, and 2–5% carbohydrates, with surfactant phospholipids being the main component regulating surface tension [9].

Decreased surfactant levels lead to increased alveolar-capillary permeability, the penetration of inflammatory cells into the alveolar space,

decreased surfactant synthesis, and compromised ventilation processes in the lungs.

Surfactant protein A (SP-A) is an active surfactant protein with immunomodulatory properties. SP-A facilitates the phagocytosis and elimination of pathogenic microorganisms and regulates the immune response in the lungs [3,7].

Recent studies suggest that SP-A, as part of the immune system, can coordinate innate and acquired immunity components through interactions with dendritic cells and T cells, thus regulating immune responses in the lungs [1,2,4,5]

As the incidence of preterm infants with respiratory distress syndrome (RDS) and respiratory failure increases, the research on surfactant proteins becomes increasingly important [10].

The aim of the research: the research aims to determine the importance of assessing SP-A levels in the blood and tracheobronchial lavage (TBL) fluid in predicting the progression of pathological processes in the lungs in preterm infants with RDS, especially those with very low and extremely low birth weights.

Materials and methods of the research

This research was conducted among preterm infants receiving treatment in the Neonatal Intensive Care Units of various hospitals. 142 preterm infants were involved in the study. Among them, 122 infants had RDS, categorized into two groups for comparison: 80 infants with very low birth weight (Group 2) and 42 infants with extremely low birth weight (Group 3). In addition, 20 infants did not have RDS and constituted the control group (Group 1). Both groups (2 and 3) were further divided into subgroups based on the presence of RDS (Subgroups 2a and 3a) and pneumonia (Subgroups 2b and 3b).

Diagnostic procedures for enrolled infants included clinical examinations, radiography, echocardiography, hematological tests, blood gas analysis, oxygenation parameters, and consideration of prenatal history.

As part of the research, blood samples (from all infants) and TBL samples were obtained. TBL samples were collected only from infants undergoing invasive ventilation. Biological material for SP-A determination was collected on days 1–7 and 10–14 of life. Peripheral venous blood was collected in standard tubes, centrifuged at 2000 rpm for 10 minutes, and 0.5 ml of serum was prepared. TBL samples were obtained by airway suctioning: 0.5 ml of sterile 0.9% NaCl solution was instilled into the endotracheal tube, followed by aspiration. SP-A levels were determined using the Human Surfactant Protein A (SP-A) ELISA Kit from Sun Red Bio (China) and analyzed using the Medispec-6000 (RT-6000, Microplate Reader). Results were expressed in ng/ml.

The results obtained were statistically analyzed in accordance with modern recommendations. Parametric variables were analyzed using Student's t-test, non-parametric variables using the Mann–Whitney U test, and correlations using the Spearman test, all performed using the SPSS 20 package. The risk of event realization was studied t with determination of their 95% confidence intervals (95% CI). The differences were considered statistically significant at $p<0.05$.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the institution indicated in the work. The informed consent of the children's parents was obtained for conducting the studies.

Results of the research and discussion

The comparative analysis of indicators across groups, including anthropometric measurements, gestational age, Apgar and Silverman scores, and the administration of adjunctive surfactant therapy as depicted in Table 1, revealed their respective influences. Taking into account birth weights, gestational ages, and Silverman scores, surfactant therapy (Curosurf) was administered at a dose of 200 mg/kg, followed by a repeat dose of 100 mg/kg for the treatment and prevention of RDS. The reapplication of exogenous surfactant was associated with ventilation compromise, hypercapnia, hypoxemia, and the need for oxygen supplementation due to the underdevelopment of the morphofunctional status of the lungs (Table 1).

The level of SP-A in venous blood was determined in a part of children involved in the study (15 newborns from group 1; 54 newborns from group 2 and 36 newborns from group 3). It was 2.9±2.3 ng/ml (95% CI 4.2–1.6) in the first group, where respiratory distress was not observed during the initial examination. In addition, when comparing subgroups: in subgroup 2b, the level of SP-A was 21.2 ng/ml (95% CI 30.8–11.5), which was 7.1 times higher compared to subgroup 2a ($p<0.01$). In subgroup 2b, compared to subgroup 2a, where the SP-A level was 6.01 ng/ml (95% CI 9.6–2.4), the difference was 3.5 times higher ($p<0.01$). Among the subgroups of group

Table 1

Comparison of physical indicators (birth weight, height) and the comparison of Gestational age, Apgar score, and Silverman scale indicators by groups, as well as the promptness of surfactant therapy application by groups

Characteristics		Group 1 (n=20)	Group 2 (n=80)	Group 3 (n=42)
Birth weight		1419.0±100.5	1324.0±128.0**	867.6±143.8*^
Height		41.4±3.2	39.0±2.8**	33.2±3.7*^
Gestational age		31.75±0.55	30.36±1.71*	27.92±2.73*^
Apgar score	1st min	5.7±1.1	5.0±1.4	2.7±1.6*^
	5th min	6.6±0.8	6.0±1.1***	4.4±1.3*^
	20th min	8.0±0.5	7.3±0.9*	6.0±1.1*^
Silverman score		0.2±0.4	5.3±2.0*	6.9±1.6*^
Surfactant therapy	1 time	–	31 (21.8%)	31 (21.8%)
	Again	–	19 (13.4%)	31 (21.8%)

Note: Compared to the Group 1: * — p<0.001, ** — p<0.01, *** — p<0.05; comparison between groups 2 and 3: ^ — p<0.001.

Table 2

SP-A levels in the initial examination

Groups		N	Mean±SD	Std. error	95% Confidence Interval for		Min	Max
					Lower bound	Upper bound		
1		15	2.98±2.36	0.61066	1.6743	4.2937	0.80	8.00
2	2a	28	6.01±9.25	1.74908	2.4290	9.6067	0.70	36.00
	2b	26	21.20±23.95*^	4.69826	11.5314	30.8839	0.40	87.00
3	3a	30	7.40±10.19	1.95670	4.2323	12.2245	0.60	44.00
	3b	6	23.78±34.82	14.21737	-12.7636	60.3302	0.80	82.00

Note: p<0.01 for comparison between 1 and 2b, and p<0.01 for comparison between 2a and 2b.

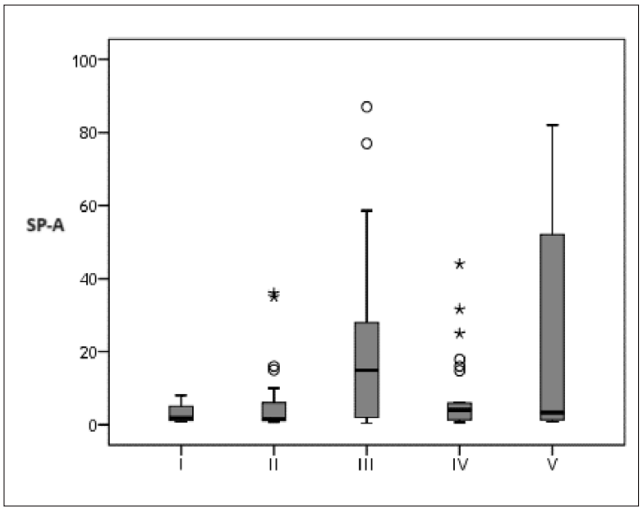
3, in subgroup 3b, where the SP-A level was 23.7 ng/ml (95% CI 60.3–12.7), the difference was 3.2 times higher compared to subgroup 3a, where the SP-A level was 7.4 ng/ml (95% CI 12.2–4.2). This indicates that SP-A level in infants born very low and extremely low birth weight, especially those who developed respiratory distress, particularly pneumonia, due to the increased permeability of the air-blood barrier, leading to an increase in SP-A levels in the blood (Table 2).

The level of SP-A in venous blood (Fig. 1) was determined to be 2.9±2.3 ng/ml (95% confidence interval (CI) 4.2–1.6) during the initial examination in the first group, where respiratory distress was not observed. Furthermore, when comparing subgroups: in subgroup 2b of the patient group, the level of SP-A was 21.2 ng/ml (95% CI 30.8–11.5), which was 7.1 times higher compared to the first group (p<0.01). Among the subgroups of the second group, the difference was 3.5 times higher (p<0.01) between subgroup 2b, where the SP-A level was 21.2 ng/ml (95% CI 30.8–11.5), and subgroup 2a, where the SP-A level was 6.01 ng/ml (95% CI 9.6–2.4). Similarly, among subgroups of the third group, the difference was determined to be 3.2 times higher (p<0.01) between subgroup 3b, where the SP-A level was 23.7 ng/ml (95% CI 60.3–12.7), and subgroup 3a, where the SP-A level was 7.4 ng/ml (95% CI 12.2–4.2). This indicates that in very low and extremely low birth weight infants, especially those who developed respiratory distress, particularly pneumonia, the level of SP-A increased due to increased permeability of the blood-air barrier, leading to an increase in SP-A levels in the blood.

During the repeat examination of SP-A in venous blood in both groups with respiratory distress: in subgroup 2a, the level of SP-A was 34.5 ng/ml (95% CI 409.3–340.3), while in subgroup 2b, it was 17.5 ng/ml (95% CI 35.87–0.71), indicating a 1.9-fold difference. In subgroup 3b, the level of SP-A was 17.4 ng/ml (95% CI 81.1–46.3), whereas in subgroup 3a, it was 14.7 ng/ml (95% CI 42.7–14.4), resulting in a 1.2-fold difference in SP-A levels. Statistical significance was not determined between subgroups during the repeat examination. Among 17 patients who received respiratory support during artificial ventilation (invasive), aspirates were obtained during TBL. In subgroup 3a, the level of SP-A in the aspirate was 13.8 ng/ml (95% CI 15.6–-11.9), while in subgroup 2a, it was 8.4 ng/ml (95% CI 54.1–37.3), indicating a 1.6-fold difference.

A direct correlation is observed between the level of SP-A in the blood of patients with respiratory distress and the oxygen dependency of the patients (r=0.240, p<0.05) (Figure 2).

In these patients, the dynamic increase in the level of C-reactive protein (CRP), considered as an



Notes: I — the group 1 (control); II — the subgroup 2a; III — the subgroup 2b; IV — the subgroup 3a; V — the subgroup 3b.

Fig. 1. The level of SP-A in venous blood in study groups, ng/ml

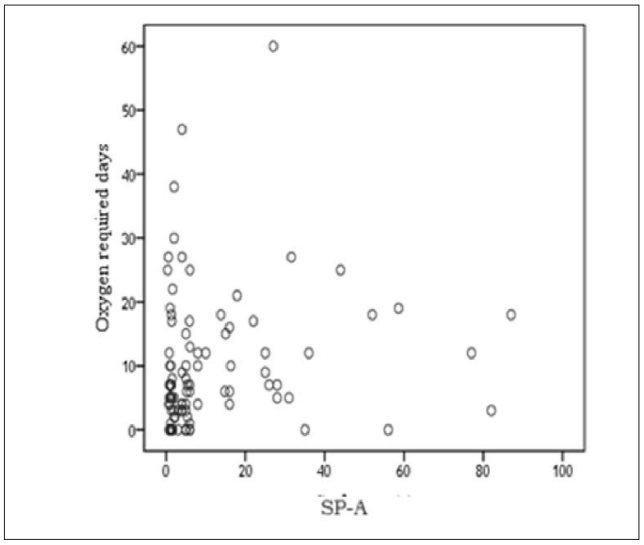


Fig. 2. Relationship between the duration of patients' oxygen dependency and SP-A levels, p<0.05

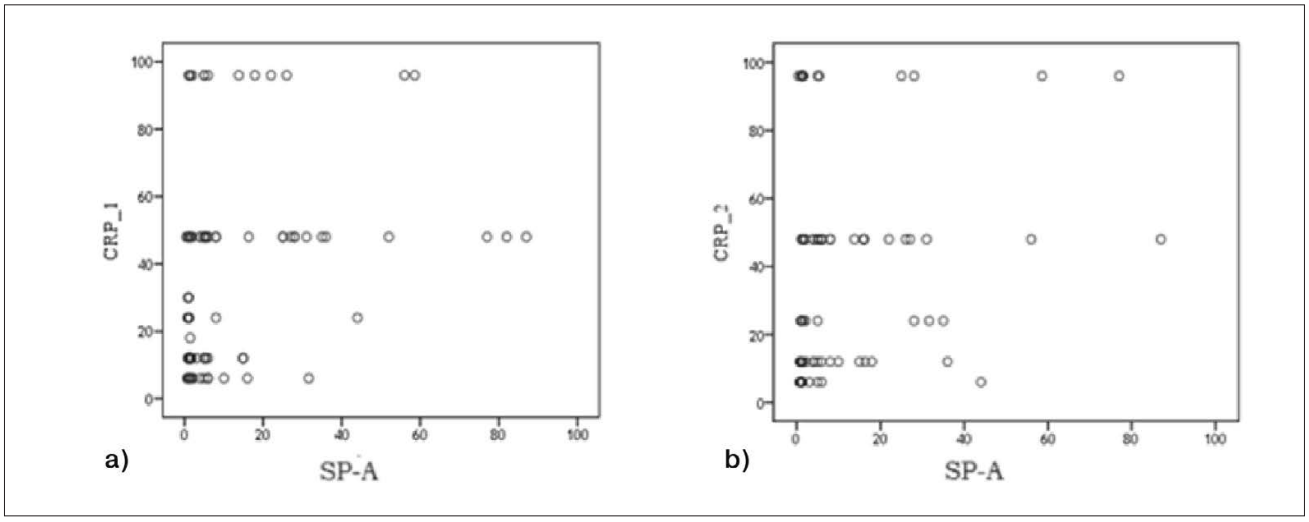


Fig. 3. Relationship between initial (a) and dynamic (b) level of CRP and SP-A, p<0.01

additional diagnostic biomarker, was investigated, and a direct correlation was determined between the level of SP-A in the blood and CRP dynamics, CRP1 (CRP at initial measurement) (r=0.339, p<0.01), CRP2 (CRP in dynamic measurement) (r=0.314, p<0.01) (Figure 3).

In the study, to understand the prognostic significance of SP-A, its levels were comparatively studied in a subgroup of children in relation to survival. We analyzed deceased and alive infants (in total 105 infants), and the results are presented in Table 3. A 1.3-fold increase in SP-A levels was observed in deceased patients compared to survivors during the initial examination, and a 2.9-fold increase was observed during repeat examinations. This indicates impairment of barrier function in the lungs, enhanced proliferation of type II alveolar cells, increased synthesis of SP-A, and continuous passage of SP-A into the blood. Conversely, in survivors, a 2.3-fold increase in SP-A levels during TBL indicates increased surfactant synthesis, enhanced immune defense, and lower capillary membrane permeability in the alveoli compared to the deceased (Table 3)

The presence of SP-A at a certain level in preterm infants without RDS is associated with superior chemical composition during surfactant synthesis and airway barrier permeability. During the dynamics of respiratory distress, the increase in the level of this protein in the blood led to structural damage to type II alveolar cells, especially increasing the permeability of the airway barrier during inflammatory processes. Therefore, compared to patients with RDS, those with pneumonia

Table 3

SP-A levels in blood and TBL in died and surviving infants

Parameter		n	Mean±SD	95% Confidence Interval for		Std. Error	Min	Max	P-values
				Lower bound	Upper bound				
SP-A initial examination	Deceased	44	12.7±18.3	7.12–18.31		2.77	0.40	82.00	p=0.052
	Alive	61	9.34±16.68	5.06–13.61		2.13	0.60	87.00	
SP-A reexamination	Deceased	8	29.21±27.22	6.45–51.96		9.62	1.20	68.00	p=0.091
	Alive	9	9.78±14.35	7.12–30.73		5.56	1.20	47.00	
TBL	Deceased	14	12.87±3.67	10.75–15.00		0.98	4.80	18.30	p=0.449
	Alive	3	29.70±29.11	-42.610–102.01		16.80	12.0	63.30	

had higher levels of SP-A in their blood. Such patients required increased artificial ventilation and oxygen dependency, while invasive procedures and hospital-acquired infections triggered by early-onset pneumonia led to an increase in CRP levels. An increase of SP-A levels in patients diagnosed with pneumonia during tracheobronchial lavage, as well as in extremely low birth weight infants diagnosed with RDS, indicated damage to the alveolar wall and activation of lung immune defense functions.

Conclusion

Particularly in very low birth weight infants, the early neonatal elevation of SP-A levels compared to those with pneumonia and RDS, the correlation with CRP, and the higher levels in deceased infants highlight the differential diagnostic and prognostic importance of SP-A during respiratory distress.

No conflict of interests was declared by the authors.

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