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Association between plasma surfactant proteins A and D levels and types of respiratory therapy in preterm neonates

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Surfactant proteins A (SP-A) and D (SP-D) are key components of the pulmonary surfactant system and play important roles in lung immunity and homeostasis. Their plasma levels may reflect pulmonary maturity and disease severity in preterm neonates.
Aim: to evaluate the association between plasma levels of SP-A and SP-D and the type of respiratory therapy administered to preterm neonates.
Material and methods. A total of 114 preterm neonates treated in multiple neonatal intensive care units (NICUs) were categorized based on initial respiratory support – non-invasive (e.g., CPAP, NIPPV) or invasive ventilation. Plasma SP-A and SP-D levels were measured using ELISA. The statistical analysis was performed to assess correlations with therapy type, diagnosis, and outcomes.
Results. Of the neonates initially managed with non-invasive therapy, 60.6% required escalation to invasive ventilation. Plasma SP-A and SP-D levels were significantly higher in those requiring invasive support compared to those maintained on non-invasive therapy. Repeated surfactant dosing and lower APGAR scores were also associated with elevated protein levels and escalation therapy. Although trends were observed in the group initially receiving invasive ventilation, statistical significance was limited by the small sample size.
Conclusion. Elevated plasma SP-A and SP-D levels are associated with an increased need for invasive respiratory support in preterm neonates. These proteins may serve as useful biomarkers for predicting respiratory therapy needs and monitoring treatment responses. Further large-scale studies are needed to validate their clinical utility.
The research was carried out in accordance with the principles of the Declaration of Helsinki. The informed consent of the patient was obtained for conducting the studies.
No conflict of interests was declared by the authors.
Keywords: respiratory distress syndrome, preterm infants, surfactant proteins, surfactant proteins D, surfactant proteins A, respiratory therapy.

Зв'язок між рівнями сурфактантних білків A та D у плазмі крові та типами респіраторної терапії у недоношених новонароджених

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Сурфактантні білки A (SP-A) та D (SP-D) є ключовими компонентами легеневої сурфактантної системи та відіграють важливу роль в імунітеті та гомеостазі легень. Їхні рівні у плазмі можуть відображати зрілість легень та тяжкість захворювання в недоношених новонароджених.
Мета: оцінити зв'язок між рівнями SP-A та SP-D у плазмі крові та типом респіраторної терапії, що застосовується недоношеним новонародженим.
Матеріали та методи. Загалом 114 недоношених новонароджених, які лікувалися в кількох відділеннях інтенсивної терапії новонароджених, було класифіковано на основі початкової респіраторної підтримки – неінвазивна (наприклад, CPAP, NIPPV) або інвазивна вентиляція. Рівні SP-A та SP-D у плазмі виміряно за допомогою ELISA. Проведено статистичний аналіз для оцінки кореляції з типом терапії, діагнозом та результатами.
Результати. З новонароджених, які спочатку отримували неінвазивну терапію, 60,6% потребували ескалації до інвазивної вентиляції. Рівні SP-A та SP-D у плазмі були значно вищими в тих, хто потребував інвазивної підтримки, порівнюючи з тими, хто отримував неінвазивну терапію. Повторне дозування сурфактанту та нижчі бали за шкалою APGAR також були пов'язані з підвищеним рівнем білка та ескалацією терапії. Попри те, що простежувалися тенденції у групі, яка спочатку отримувала інвазивну вентиляцію, статистична значущість була обмежена невеликим розміром вибірки.
Висновок. Підвищені рівні SP-A та SP-D у плазмі пов'язані зі збільшенням потреби в інвазивній респіраторній підтримці в недоношених новонароджених. Ці білки можуть бути корисними біомаркерами для прогнозування потреб у респіраторній терапії та моніторингу відповідей на лікування. Для підтвердження їхньої клінічної корисності необхідні подальші масштабні дослідження.
Дослідження виконано за принципами Гельсінської декларації. На проведення досліджень отримано інформовану згоду батьків дитини.
Автори заявляють про відсутність конфлікту інтересів.
Ключові слова: респіраторний дистрес-синдром, недоношені діти, сурфактантні білки, сурфактантні білки D, сурфактантні білки A, респіраторна терапія.

Introduction

Immaturity of the lungs and immune systems is a significant risk factor for increased morbidity and mortality in preterm infants. Surfactant proteins A (SP-A) and D (SP-D) are pulmonary immune molecules that create a link between these two systems and are involved in neutralizing pathogens and modulating inflammatory responses. Additionally, SP-A enhances the function of SP-B and SP-C proteins and preserves the integrity of densely packed lipid-protein complexes [1,4–6]. This optimizes surfactant function under challenging physiological conditions and prevents its inhibition by serum components. SP-D plays a key role in stimulating the overproduction of surfactants during processes of surfactant homeostasis disruption [3].

SP-A and SP-D play a major role in maintaining the lungs in a non-inflammatory and infection-free homeostatic state, ensuring effective gas exchange.

The highest incidence of respiratory distress syndrome (RDS) and its consequence, bronchopulmonary dysplasia (BPD), is observed particularly in extremely preterm infants. The majority of these extremely low birth weight neonates require respiratory support in the first days of life [2].

Modern technologies for successful RDS management involve the rational use of oxygen therapy and a combination of various respiratory support methods. These include continuous positive airway pressure (CPAP) with spontaneous breathing and variable flow, conventional mechanical ventilation (MV) in various modes, and high-frequency oscillatory ventilation (HFOV). These methods, in combination with surfactant therapy, enable effective treatment of RDS.

In recent years, early application of non-invasive CPAP and surfactant therapy has come to the forefront in RDS treatment. However, treatment fails in about half of the preterm infants assigned to CPAP, requiring intubation, which increases the risk of BPD and pneumothorax. CPAP is considered an optimal support method for newborns who do not require intubation and helps prevent respiratory failure after extubation, although it does not affect oxygen dependence on the 28th day [7]. MV remains one of the most effective methods for treating respiratory failure in preterm infants with either RDS or pneumonia.

However, the positive effects of MV, related to increased intrathoracic pressure and the opening of atelectasis, can very quickly lead to adverse outcomes. These include complications such as BPD and air leak syndromes, which are associated with barotrauma and high oxygen concentration [2]. As a result, surfactant synthesis is disrupted, and the synthesized surfactant becomes inactivated. Therefore, both quantitative and qualitative disturbances in surfactants are central to the pathogenesis of respiratory disorders in preterm infants [3].

The primary ***aim*** of this study was to investigate the relationship between plasma levels of SP-A and SP-D and the type of respiratory therapy administered to preterm neonates.

Materials and methods of the study

This study included 114 preterm neonates who received treatment in the neonatal intensive care units (NICUs) of the Scientific Research Institute of Paediatrics, the Institute of Obstetrics and Gynaecology, the Republican Clinical Hospital, and the Perinatal Centre. Based on the type of initial respiratory therapy, patients were divided into two groups: those receiving non-invasive ventilation (e.g., CPAP and NIPPV – Nasal Intermittent Positive Pressure Ventilation) and those requiring invasive MV. Within each group, the dynamic requirement for respiratory therapy was assessed about plasma levels of SP-A and SP-D.

Peripheral venous blood samples 1 mL) were collected into standard test tubes. After centrifugation at 2000 rpm for 10 minutes, 0.5 mL of serum was extracted for analysis. Plasma SP-D and SP-A levels were measured using a commercial Human SP-D ELISA Kit (Sun Red Bio, China), and absorbance was read using the Medispec-6000 microplate reader (RT-6000). Results were expressed in ng/mL. A 95% confidential interval (95% CI) was determined. The results were considered significant at $p<0.05$.

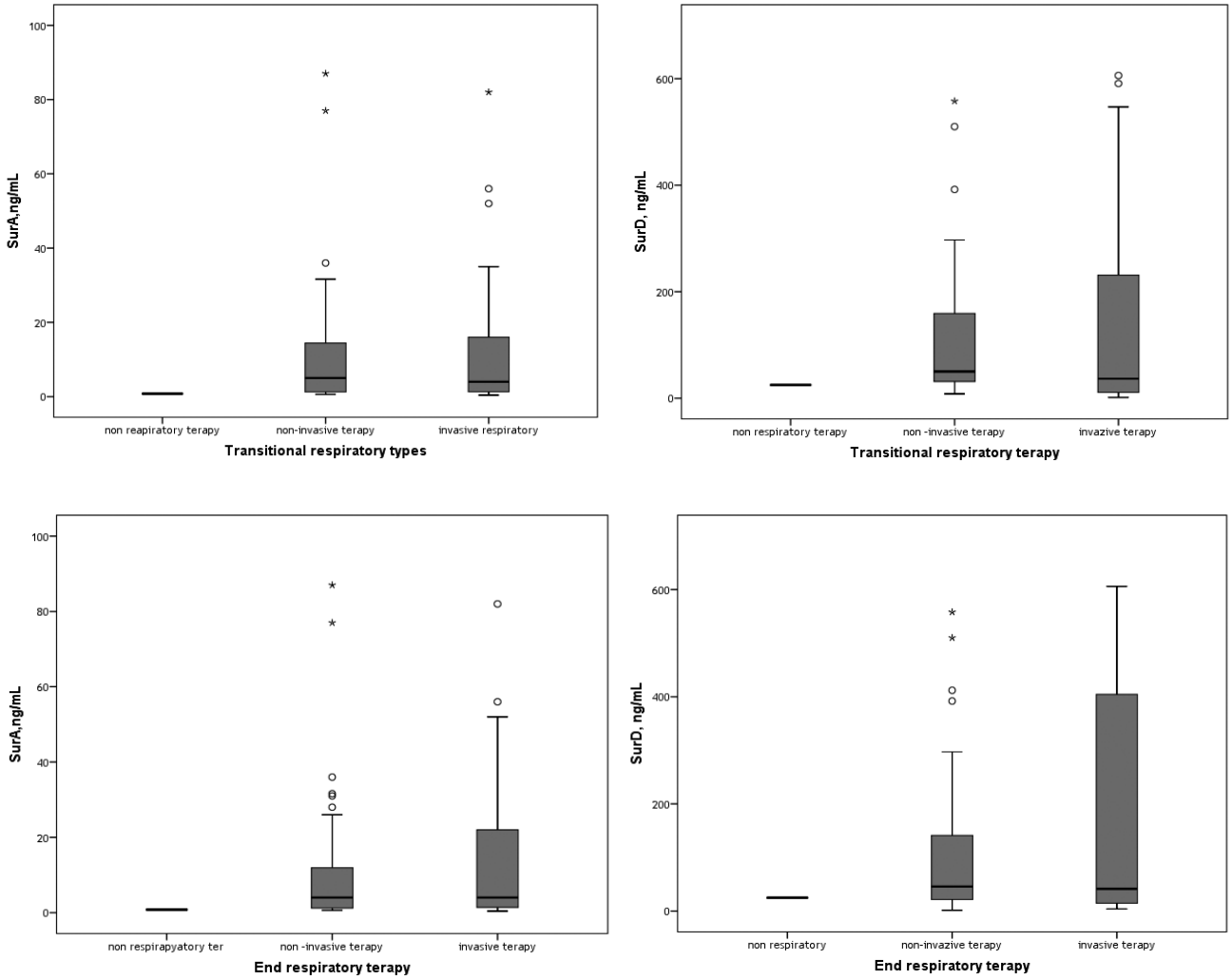
Data were statistically analyzed according to contemporary recommendations using SPSS version 20. For parametric data with normal distribution, Student's t-test was used, while the Mann–Whitney U test was applied for non-parametric data. Correlation analyses were performed using Spearman's rank correlation coefficient.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The informed consent of the patient was obtained for conducting the studies.

Results of the study and discussion

Of the 114 neonates, 94 initially received non-invasive respiratory support. Among these, 46 neonates (49%) had very low birth weight (VLBW) and RDS, 21 neonates (22%) had VLBW and pneumonia, 20 neonates (21%) had extremely low birth weight (ELBW) with RDS, and 7 neonates (7.4%) had ELBW with pneumonia. Non-invasive therapy was successfully continued in 36 neonates, while 57 required the escalation to invasive MV.

SP-A levels were measured in 64 neonates, and SP-D in 61 neonates. Of those who transitioned to invasive therapy, 24 (42%) had VLBW-RDS, 14 (25%) had VLBW-pneumonia, 15 (26%) had ELBW-RDS, and 4 (7%) had ELBW-pneumonia. The association between diagnosis and need for invasive therapy was statistically significant ($\chi^2=16$, $df=6$, $p<0.05$).



Note: SurA – SpA, Sur D – SpD.

Fig. 1. Surfactant therapy and respiratory support outcomes: surfactant proteins A and D plasma levels related to respiratory types

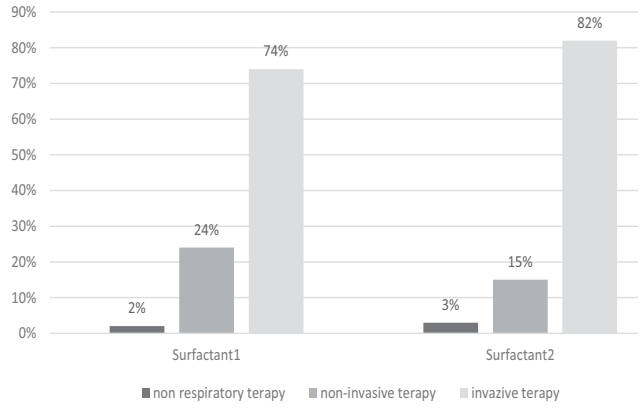
A comparison of SP-A and SP-D levels between neonates who continued on non-invasive therapy and those who transitioned to invasive therapy revealed significantly higher levels of both proteins in the latter group. A graphical analysis supported these findings (Figure 1).

Neonates receiving exogenous surfactant therapy were more likely to require invasive ventilation. Specifically, 74% (n=34) of neonates who received initial surfactant instillation required invasive ventilation, compared to 48% (n=23) of neonates who did not receive surfactant (χ^2=8.5, df=2, p=0.014) (Figure 2).

In total, 46 of the neonates initially receiving non-invasive therapy were administered surfactant. These neonates were predominantly from the VLBW-RDS subgroup (χ^2=7.1, df=3, p=0.069). A second dose of surfactant was required in 34 neonates, primarily among those with VLBW-RDS and ELBW-RDS (χ^2=14, df=3, p=0.003). Among those receiving a second surfactant dose, 28 (82.4%) required transition to invasive therapy (χ^2=13.6, df=2, p=0.001), indicating a strong association between repeat dosing and progression to invasive ventilation. Figure 3 illustrates the dynamics of respiratory therapy among neonates initially managed with non-invasive support and subsequently treated with surfactant.

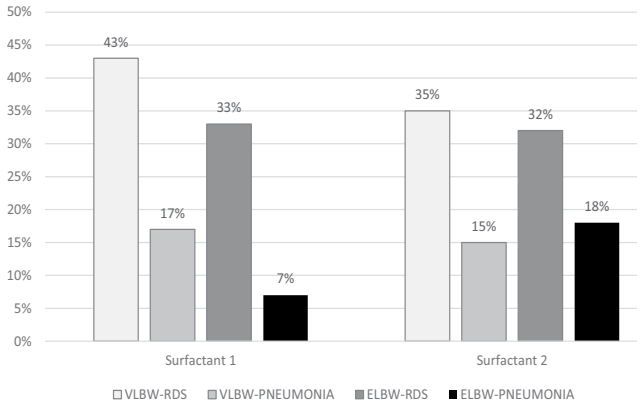
APGAR scores and therapy escalation

Neonates requiring escalation to invasive therapy had lower APGAR scores at both 5 and 20 minutes post-delivery. At 5 minutes, the APGAR score was 3.9±1.9 (95% CI: 3.5–4.5) in the invasive group, versus 5.0±1.5 (95% CI: 4.5–5.4) in the non-invasive group (p=0.32). At 20 minutes, the mean APGAR score in the invasive group was 6.8±1.02 (95% CI: 6.5–7.1), significantly lower than in the non-invasive group (7.4±1.0; 95% CI: 7.0–7.7; p=0.041).



Notes: Surfactant 1 – first dose of surfactant; Surfactant 2 – second dose of surfactant.

Fig. 2. Transitional respiratory therapy in neonates who initially received non-invasive therapy and surfactant instillation



Notes: Surfactant 1 – first dose of surfactant; Surfactant 2 – second dose of surfactant.

Fig. 3. Group-wise proportion of children who received surfactant therapy

Among the 57 neonates who required invasive therapy during the course of treatment, 11 (19.3%) were successfully weaned to non-invasive support, while 46 (80.7%) continued with invasive MV. Plasma SP-A and SP-D levels were compared between these subgroups. In those weaned to non-invasive therapy (n=8), the median SP-A level was 1.5 ng/mL, while in those continuing invasive therapy (n=28), the median level was 4.5 ng/mL. Similarly, SP-D levels were 19 ng/mL and 41.5 ng/mL in these groups, respectively.

Initial invasive therapy group

Initial invasive respiratory support was required in 20 neonates. Of these, 1 (5%) neonate had VLBW-RDS, 4 (20%) had VLBW-pneumonia, and 15 (75%) had ELBW-RDS. All neonates diagnosed with ELBW-pneumonia were initially managed with non-invasive or supplemental oxygen therapy.

Among the 20 initially invasively ventilated neonates, 7 (35%) were subsequently weaned to non-invasive support, while 13 (65%) remained on invasive ventilation. Two of the 7 (28.6%) non-invasive cases later required reintubation. Thus, of those who began with invasive therapy, 5 (25%) were successfully weaned, and 15 (75%) required ongoing invasive support.

SP-A and SP-D levels were analyzed in these neonates according to therapy type. In the non-invasive group (n=4), the median SP-A level was 9.5 ng/mL (range: 43 ng/mL), while in the invasive group, it was 5.3 ng/mL (range: 55.6 ng/mL). For SP-D, the corresponding median levels were 292.5 ng/mL (n=4, range: 567ng/mL) and 27 ng/mL (n=11, range: 787ng/mL), respectively. These differences were not statistically significant ($p>0.05$), likely due to small sample sizes.

Our findings demonstrate a clear association between elevated plasma SP-A and SP-D levels and the need for more intensive respiratory support, particularly invasive ventilation. These surfactant proteins may serve not only as biomarkers of lung maturity and disease severity but also as predictive markers for the escalation of therapy in preterm neonates.

Higher levels of SP-A and SP-D were consistently associated with greater clinical instability, poorer APGAR scores, and a higher likelihood of receiving multiple doses of exogenous surfactant. These findings align with existing literature indicating elevated surfactant protein levels in inflammatory or compromised lung conditions.

While the relationship between surfactant protein levels and therapy type was evident in most subgroups, the lack of statistical significance in certain comparisons may be attributed to small sample sizes and variable clinical conditions.

Conclusion

Plasma levels of surfactant proteins A and D are significantly associated with the type and intensity of respiratory therapy required in preterm neonates. These biomarkers may be useful in predicting the need for escalation from non-invasive to invasive ventilation and assessing the response to surfactant therapy. Further large-scale, prospective studies are warranted to validate the clinical utility of SP-A and SP-D measurements in the NICU setting.

No conflict of interests was declared by the authors.

REFERENCES/ЛІТЕРАТУРА

1. Bersani I, Speer CP, Kunzmann S. (2012, May). Surfactant proteins A and D in pulmonary diseases of preterm infants. Expert Rev Anti Infect Ther. 10(5): 573-584. doi: 10.1586/eri.12.34. PMID: 22702321.
2. Hentschel R, Bohlin K, van Kaam A et al. (2020). Surfactant replacement therapy: from biological basis to current clinical practice. Pediatr Res. 88: 176-183. https://doi.org/10.1038/s41390-020-0750-8.
3. Kaltsogianni O, Dassios T, Greenough A. (2023). Neonatal respiratory support strategies — short and long-term respiratory outcomes. Front. Pediatr. 11: 1212074. doi:10.3389/fped.2023.1212074.
4. Mapindra MP, Castillo-Hernandez T, Clark H, Madsen J. (2025, Jan 1). Surfactant Protein-A and its immunomodulatory roles in infant respiratory syncytial virus infection: a potential for therapeutic intervention? Am J Physiol Lung Cell Mol Physiol. 328(1): L179-L196. Epub 2024 Dec 11. doi: 10.1152/ajplung.00199.2024. PMID: 39662519
5. Pastva AM, Wright JR, Williams KL. (2007, Jul). Immunomodulatory roles of surfactant proteins A and D: implications in lung disease. Proc Am Thorac Soc. 4(3): 252-7. doi: 10.1513/pats.200701-018AW. PMID: 17607008; PMCID: PMC2647627.
6. Watson A, Madsen J and Clark HW. (2021). SP-A and SP-D: Dual Functioning Immune Molecules With Antiviral and Immunomodulatory Properties. Front. Immunol. 11: 622598. doi: 10.3389/fimmu.2020.622598.
7. Yue G, Wang J, Li H, Li B, Ju R. (2021, Jul 30). Risk Factors of Mechanical Ventilation in Premature Infants During Hospitalization. Ther Clin Risk Manag. 17: 777-787. doi: 10.2147/TCRM.S318272. PMID: 34354359; PMCID: PMC8331080.

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