

Influence of Natural Lung Surfactant Inhalations on Clinical Symptoms and Pulmonary Function Parameters in Patients with Bronchial Asthma. Communication 2

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Abstract

Background: Damage to lung surfactant (LS) enabling the lung local immunity may contribute to the development of bronchial inflammation in patients with bronchial asthma (BA).

Methods and Results: A 70-day course of 21 LS (Surfactant-BL) inhalations at the dose of 25 mg was added to inhaled corticosteroids (ICS) and short/long-acting bronchodilators or combined inhalers in 13 BA patients. After 21 inhalations, many patients reported lower frequency of cough and profuse expectoration, fewer night and day attacks, resolution of wheezing, resolution or lower frequency of bronchospasm episodes under moderate exercise, and termination (1 patient) or double reduction (8 patients out of 13) of the ICS dose. The values of pulmonary function parameters in patients at Days 250 and 340 did not differ significantly from the values achieved at Day 41. The mean values at Days 250 and 340 were as follows: FVC = 86.4±6.43%, FEV1 = 61.4±8.41%, FEV1/FVC = 66.5±8.87%.

Conclusion: LS inhalations improve the condition of patients with BA, allow ICS dose reduction by 2 times, and improve pulmonary function parameters. A total of 70% of patients had quite a long remission of BA symptoms following a 21-inhalation therapy course of the formulation. (**International Journal of Biomedicine. 2017;7(3):167-170.**)

Key Words: lung surfactant • bronchial asthma • inhaled corticosteroids • dose • pulmonary function

Abbreviations

BA, bronchial asthma; ICS, inhaled corticosteroids; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LS, lung surfactant; PFPs, pulmonary function parameters.

Introduction

Deficiency or qualitative changes in lung surfactant (LS) are found in many lung conditions, including bronchial asthma (BA).^(1,2) Apart from enabling the breathing mechanism, LS

is known to provide molecular mechanisms of innate and adaptive lung tissue immunity and to have anti-inflammatory properties.^(3,4) Aside from the review by Hohlfeld⁽⁵⁾ discussing in detail the role of LS system impairment and the possible use of LS formulations for BA, little research has been carried out so far to investigate the possibility of restoring pulmonary function and achieving stable improvement of clinical manifestations in BA patients by inhaled LS formulations.

In our earlier work, we showed that long-term inhalations of prednisolone hemisuccinate significantly decrease lung

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surfactant levels in rats, and we hypothesized that inhalations of natural formulations of lung surfactant will stimulate the synthesis of endogenous surfactant and weaken dependency on ICS in BA patients.⁽⁶⁾

Our previous article demonstrated that a course of natural LS inhalations, given as part of combined therapy for patients with BA, leads to significant improvement of clinical manifestations and PFPs. The 41-day surfactant therapy course consisting of 16 inhalations has allowed ICS dose reduction by 2 times.⁽⁷⁾

The objective of this study was to evaluate the effectiveness of surfactant treatment based on the evaluation of clinical manifestations in BA patients who have received a course of surfactant therapy comprising 21 inhalations of Surfactant-BL (Biosurf, Russia) over 70 days and who have been followed up for 340 days.

Materials and Methods

We examined 13 patients (one was withdrawn from the study having moved to another city) with partly controlled and uncontrolled persistent BA at the Pulmonary Center of Chita Road Clinical Hospital. The clinical trial was carried out based on the decision of the Local Ethical Committee under the Chita State Medical Academy and according to the approved Protocol. The enrolled patients were diagnosed according to the 2016 GINA guidelines⁽⁸⁾ and had had a history of asthma for a period of time varying from 6 months to 24 years. The study was conducted from January 20, 2016 to December 30, 2016. The treatment they had been receiving prior to their entry into the study included antibiotics during exacerbations, with 8 out of 13 patients receiving short courses of systemic per-oral and/or parenteral glucocorticoids. After their condition became stable, they had received either inhaled ICS and short/long-acting bronchodilators or combined inhalers for 12 months to 12 years prior to enrollment. Upon enrollment, the patients started a course of inhalations with Surfactant-BL (OOO Biosurf, Saint Petersburg, Russia), a natural LS formulation, at the dose of 25 mg per inhalation. The surfactant was administered using the compressor nebulizer Boreal (Italy). The patients were instructed how to use it at the first visit (V1) and then continued to use it on their own for inhalations at home. The surfactant was taken daily for the first 7 days of the study and then at Days 10, 13, 16, 19, 22, 26, 30, 35, 41, 47, 54, 61, 68 and 70 (a total of 21 inhalations). Patients were examined over the whole study period at 9 visits on Days 1(V1), 8(V2), 15(V3), 29(V4), 41(V5), 70(V6), 160(V7), 250(V8) and 340(V9). At each visit, the clinical condition of the patient was evaluated, including frequency of bronchospasm episodes, cough, wheezing, profuse expectoration, shortness of breath with exercise and speaking, and frequency of attacks while sleeping.

Statistical analysis was performed using the statistical software «Statistica» (v6.0, StatSoft, USA). The mean (M) and standard error of the mean (SEM) were calculated. Student's unpaired and paired t-tests were used to compare mean values for data with normal distribution. Regression analysis was performed by the least squares method. The statistical

significance of the b coefficients of the linear regression equations was evaluated using Student's t-test. A probability value of $P < 0.05$ was considered statistically significant.

Results

Earlier we demonstrated that after 7 inhalations (V2) wheezing stopped and frequency of attacks decreased in most patients, as did shortness of breath and bronchospasm episodes under strenuous exertion.⁽⁷⁾

Follow-up according to the Protocol allowed us to evaluate the dynamics of BA clinical manifestations after 21 inhalations (Day 70) and at the following 9 visits, in comparison with the baseline. The results of the evaluation are presented in Table 1. Data show a significant decrease in patients complaining of nocturnal attacks, profuse expectoration, cough, and wheezing after the 21 surfactant inhalations of a 70-day therapy course. Patient condition continued to improve over the complete follow-up period, and by Day 340 the number of patients complaining of the above symptoms and of attacks under exertion and day attacks as compared to baseline had significantly decreased. A double reduction of the ICS dose was achieved for 8 patients out of 13, while 2 other patients stopped taking ICS and only 3 patients out of 13 had to continue receiving the same ICS dose. The above data show that the decrease or resolution of BA symptoms holds steadily over 10 months after termination of a surfactant therapy course.

Figure 1 demonstrates the dynamics of the percentage of patients showing resolution or decreased severity of BA symptoms as represented by the solid line ("Improvement") from baseline to Day 70. The dynamics of ICS dose decrease was evaluated over the same time period for the same patients and is represented by the dotted line ("ICS") in the figure. Both parameters change exponentially, the "Improvement" line equation being $\lg y = 1.45 + 0.012 \cdot x$ ($P < 0.05$), and the "ICS" line equation being $\lg y = 1.98 + 0.003 \cdot x$ ($P < 0.01$).

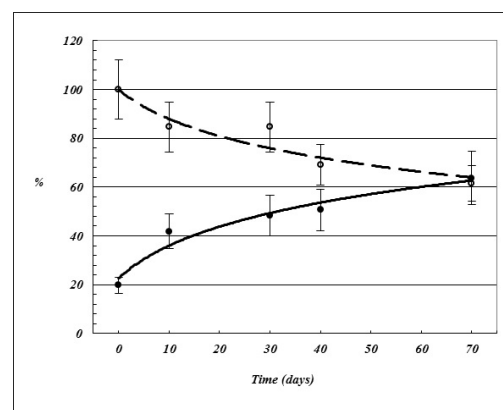


Fig. 1. The dynamics of the percentage of patients showing improvement of their clinical condition (solid line) and of the decrease of the ICS dose taken by the patients (dotted line) during the 70-day surfactant therapy course accompanied by combined treatment with ICS and bronchodilators.

Table 1.

BA symptom frequency dynamics after the termination of Surfactant-BL inhalations (Day 70) and at the end of the follow-up period (340 days)

| Symptom (complaint) | Number of patients having the symptom at baseline (%)* | Number of patients having the symptom after Visit 6 (Day 70) (%)* | P | Number of patients having the symptom at the end of the follow-up period (Day 340) (%)* | P |
|-------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------------------|--------|-----------------------------------------------------------------------------------------|--------|
| Bronchospasm under exertion | 46.2±14.39 | 15.4±10.42 | >0.05 | 0.0±0.00 | <0.01 |
| Nocturnal attacks | 61.5±14.05 | 7.7±7.70 | <0.01 | 0.0±0.00 | <0.001 |
| Expectoration | 100.0±0.00 | 23.1±12.17 | <0.001 | 30.8±13.33 | <0.001 |
| Cough | 100.0±0.00 | 46.2±14.39 | <0.01 | 30.8±13.33 | <0.001 |
| Wheezing | 100.0±0.00 | 30.8±13.33 | <0.001 | 15.4±10.42 | <0.001 |
| Day attacks | 84.6±10.42 | 53.8±14.39 | >0.05 | 38.5±14.05 | <0.05 |
| Shortness of breath under exertion | 100.0±0.00 | 61.5±14.05 | <0.05 | 53.8±14.39 | <0.01 |
| All parameters (mean values of the mean values) | 84.6±3.24 | 34.0±4.75 | <0.001 | 24.2±4.21 | <0.001 |
| Decrease of the ICS dose | 100.0±0.00 | 61.5±14.05 | <0.05 | 23.1±12.17 | <0.001 |

Note: * - 100% is the total number of patients (n=13); P - significance of differences compared to baseline.

The data in Table 1 and Figure 1 provide evidence that surfactant-BL given as part of combined therapy with ICS and bronchodilators to BA patients results not only in a significant decrease in the frequency and severity of many BA symptoms, but also in a continual decrease in the ICS dose.

Thus, clinical data of patients with partly controlled and uncontrolled persistent BA who had received 21 inhalations of natural LS at the dose of 25 mg as add-on therapy to ICS and short/long-acting bronchodilators suggests a positive effect of surfactant therapy as part of combined therapy. As a result of this therapy, many patients reported lower frequency of cough and profuse expectoration, fewer night and day attacks, resolution of wheezing, resolution or lower frequency of bronchospasm episodes under moderate exercise, and termination (1 patient) or double reduction (8 patients out of 13) of the ICS dose.

It is also important that the objective data showing pulmonary function improvement already after 16 inhalations demonstrate significant improvement of the functional state of the bronchi.⁽⁷⁾ This improvement was confirmed during the follow-up. The values of PFPs in patients at Days 250 and 340 (V8 and V9) did not differ significantly from the values achieved at Day 41 (V5). The mean values at Days 250 and 340 (V8 and V9) were as follows: FVC = 86.4±6.43%, FEV1 = 61.4±8.41%, FEV1/FVC = 66.5±8.87%.

The data obtained from the clinical study of Surfactant-BL used for treatment of BA patients leads to a preliminary conclusion that 70% of patients had quite a long remission of BA symptoms following a 21-inhalation therapy course of the formulation.

Discussion

Earlier preclinical and clinical studies involving a limited number of patients have shown that LS formulations prevent the development of a bronchospasm when provoked by an antigen, improve PFPs, and normalize the LS phospholipid composition in BA patients.⁽⁹⁻¹²⁾ It has been found that multiple administration of phosphatidylcholine and cholesterol liposomes to rats⁽¹³⁾ and multiple administration of lung surfactant to newborn humans⁽¹⁴⁾ enhances the synthesis of endogenous surfactant by its reutilization by the alveolocytes-II. The use of surfactant in therapy and prevention of acute respiratory distress syndrome in adults⁽¹⁵⁻¹⁸⁾ and in lung tuberculosis⁽¹⁹⁻²¹⁾ has been shown to be highly effective.

It is important to further investigate why 30% of patients with partly controlled and uncontrolled persistent BA did not respond to the surfactant therapy course. The ongoing evaluation of the immunological status of the enrolled patients may be helpful in finding an answer to this question.

Competing interests

The authors declare that they have no competing interests.

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References

1. Kurashima K, Fujimura M, Matsuda T, Kobayashi T.

- Surface activity of sputum from acute asthmatic patients. *Am J Respir Crit Care Med.* 1997;155(4):1254-9.
2. Devendra G, Spragg RG. Lung surfactant in subacute pulmonary disease. *Respir Res.* 2002;3:19.
 3. van Iwaarden FJ, van Golde LMJ. Pulmonary surfactant and lung defense. In: Robertson B, Taeusch HW, editors. *Surfactant therapy for lung disease. Lung biology in health and disease. Vol. 84.* New York: Marcel Dekker Inc; 1995:75-84.
 4. Rozenberg OA. Pulmonary Surfactants for Acute and Chronic Lung Diseases (Part II). *General Reanimatology.* 2014;10(5):69-86. [in Russ].
 5. Hohlfeld J, Fabel H, Hamm H. The role of pulmonary surfactant in obstructive airways disease. *Eur Respir J.* 1997;10(2):482-91.
 6. Rosenberg OA, Lebedeva ES, Loshakova LV, Shulga AEd, Seiliev AA, Volchkov VA. Influence of Long-Term Inhaled Glucocorticoids on the Lung Surfactant Phospholipid Levels in Rats. *International Journal of Biomedicine.* 2016;6(3):167-169.
 7. Stepanova OV, Akulova EA, Kochneva AA, Seiliev AA, Shulga AEd, Lovacheva OV, et al. Influence of Natural Lung Surfactant Inhalations on Clinical Symptoms and Pulmonary Function Parameters in Patients with Bronchial Asthma. Communication 1. *International Journal of Biomedicine.* 2016;6(4):255-258.
 8. Pocket Guide for Asthma Management and Prevention (for Adults and Children Older than 5 Years). A Pocket Guide for Health Professionals. Updated 2016. Available from: <http://ginasthma.org/wp-content/uploads/2016/05/WMS-GINA-2016-main-Pocket-Guide.pdf>
 9. Cheng G, Ueda T, Sugiyama K, Toda M, Fukuda T. Compositional and functional changes of pulmonary surfactant in a guinea-pig model of chronic asthma. *Respir Med.* 2001;95(3):180-6.
 10. Babu KS, Woodcock DA, Smith SE, Staniforth JN, Holgate ST, Conway JH. Inhaled synthetic surfactant abolishes the early allergen-induced response in asthma. *Eur Respir J.* 2003;21(6):1046-9.
 11. Kurashima K, Ogawa H, Ohka T, Fujimura M, Matsuda T, Kobayashi T. A pilot study of surfactant inhalation in the treatment of asthmatic attack. *Allergy.* 1991;40(2):160-3.
 12. Zagorul'ko AK, Nikitina NV, Askari TA, Zagorul'ko AA. Role of the pulmonary surfactant in the pathogenesis of bronchial asthma. *Lik Sprava.* 2001;(5-6):16-9. [Article in Russian]
 13. Rosenberg OA, Kirillov YA, Danilov LN, Loshakova LV, Lebedeva ES, Shylga AE, et al. The lung surfactant immune system response to intratracheal administration of "empty" liposomes. *J Liposome Research.* 1994;4(1):203-212.
 14. Soll R, Ozek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. *Cochrane Database Syst Rev.* 2009; 1: CD000141.
 15. Gregory TJ, Steinberg KP, Spragg R, Gadek JE, Hyers TM, Longmore WJ, et al. Bovine surfactant therapy for patients with acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* 1997;155(4):1309-15.
 16. Rosenberg OA, Bautin AE, Osovskikh VV, Tsibulkin EK, Gavrillin SV., Kozlov IA. When to start surfactant therapy (ST_therapy) of acute lung injury? Abstracts 11th ERS Annual Congress Berlin, Germany. September 22—26, 2001. *Eur. Respir J.* 2001;18 (Suppl 38): P153,7s.
 17. Bautin A, Khubulava G, Kozlov I, Poptzov V, Osovskikh V, Seiliev A, et al. Surfactant Therapy for Patients with ARDS after Cardiac Surgery. *J Liposome Research.* 2006;16(3):265-72.
 18. Gekkieva OV, Bautin AE, Osovskikh VV, Tregubova IV, Seiliev AA, Rosenberg OA. [Preventive Treatment with Surfactant in Thoracic Surgeries Associated with High Risk of Respiratory Failure]. *Doctor. Ru. Anesthesiology and Critical Care Medicine (Fast Track).* 2016;12(129 Part I):37-42. [Article in Russian].
 19. Lovacheva OV, Erokhin VV, Chernichenko NV, Evguschenko GV, Lepekha LN, Rosenberg OA. [Results of use of surfactant in complex therapy of patients with destructive pulmonary tuberculosis. *Probl Tuberk Bolezn Legk.* 2006;(10):12-7. [Article in Russian].
 20. Erokhin VV, Romanova LK. Lung Surfactant System. In: Erokhin VV, Romanova LK, editors. *Lung Cell Biology in Health and Pathology.* Doctors' Handbook. Moscow: Medicine; 2000:167-181.
 21. Zhemkov VF, Ivanovsky VB, Zhemkova MV, Seiliev A, Volchkov VA, Rosenberg OA. [The use of natural lung surfactant in combined therapy for lung tuberculosis]. *Tuberk Bolezn Legk.* 2013;90(2): 018-022. [Article in Russian].
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