

Nebulized rhDNase therapy in newborn infants with atelectasis

Atelektazili yenidoğan bebeklerde nebülize rhDNaz tedavisi

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Abstract

Purpose: To see the efficacy in atelectasis and clinical effectiveness of rhDNase in newborns unresponsive to conventional therapy.

Material and methods: Eight newborns (7 premature) with atelectasis in the lungs were evaluated retrospectively. All patients were given rhDNase 2.5 mg twice daily with nebulizer for up to 3 days after conventional therapies.

Results: The birth weight and gestational age of the patients ranged respectively from 500 g to 3000 g and 25 weeks to 41 weeks. When atelectasis developed, six of eight patients were mechanically ventilated. Infants received a dosage of 2.5 mg rhDNase every 12 hours with nebulizer for 3 days. Six of 8 patients showed almost complete improvement after the rhDNase treatment. One patient who did not respond to the treatment had an underlying "hypoxic ischemic encephalopathy" and complicated pneumonia. This patient died during the follow up. The other patient gave partial response to treatment. Of 6 mechanically ventilated patients 3 patients extubated in 3 days, one patient extubated after 9 days and two patients could not be extubated. Atelectasis relapsed in 6 patients. After second 3-day course of treatment by a nebulizer, recovery was seen in 3 days. There was no side effect due to rhDNase treatment.

Conclusion: We suggest that rhDNase may be administered as an alternative treatment to the newborn infants with atelectasis in their lung. Especially, if there was no underlying disease, and if they did not respond to conventional treatment for atelectasis. More studies should be done with larger study groups.

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Key words: Atelectasis, mechanical ventilaton, newborn, rhDNase.

Özet

Amaç: Geleneksel tedaviye yanıt vermeyen yenidoğanlarda rhDNaz'ın klinik olarak ve atelektazideki etkinliğini görmektir.

Gereç ve yöntem: Akciğerlerinde atelektazi olan 8 yenidoğan (7 prematüre) retrospektif olarak değerlendirilmiştir. Tüm hastalara geleneksel tedaviden sonra 3 gün boyunca günde 2 kez olmak üzere 2,5 mg dozunda rhDNaz nebülizatör ile verilmiştir.

Bulgular: Hastaların doğum kiloları ve doğum haftaları sırasıyla 500 gr-3000 gr ve 25 hafta-41 hafta arasındaydı. Atelektazi geliştiği sırada hastaların altısı mekanik ventilatördeydi. Bebekler 3 gün boyunca 2.5 mg dozunda rhDNaz, 12 saatte bir nebülizatör ile almışlardır. Sekiz hastanın altısı rhDNaz tedavisi sonrası tamamen düzelmiştir. Tedaviye yanıt vermeyen 1 hastanın alta yatan "hipoksik iskemik ensefalopati" ve komplike pnömoni hastalığı mevcuttu. Bu hasta takip sırasında kaybedilmiştir. Diğer hasta tedaviye kısmi yanıt vermiştir. Mekanik ventilasyonda olan 6 hastadan 3'ü 3 gün içerisinde, 1'i 9 gün sonra ekstübe edilmiştir. İki hasta ekstübe edilememiştir. Altı hastada atelektazi tekrarlamıştır. Üç günlük 2. kür nebülizatör ile tedaviden sonra 3 gün içerisinde düzelleme görülmüştür. rhDNaz tedavisine bağlı herhangi bir yan etki oluşmamıştır.

Sonuç: rhDNaz, akciğerlerinde atelektazi olan yenidoğan bebeklerde alternatif tedavi olarak uygulanabilir. Özellikle alta yatan herhangi bir hastalığı olmayanlara ve atelektazi için geleneksel tedaviye yanıt vermeyenlere önerilebilir. Daha fazla sayıda çalışma grubuyla çalışmalara ihtiyaç vardır.

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Anahtar sözcükler: Atelektazi, mekanik ventilator, yenidoğan, rhDNaz.

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Introduction

In respiratory distress syndrome (RDS), due to surfactant deficiency, there was a mismatching in ventilation-perfusion. Hyaline membranes and inflammation in RDS blocks small airways, causing atelectasis and over inflation [1]. Inflammation causes necrosis of epithelial cell and thick mucous production in respiratory system, leading occlusion of airway lumen [2]. This occlusion may be partial leading to air trapping and hyperinflation. But total occlusion causes atelectasis [3]. Lysis of inflammatory cells, mostly leucocytes, leads to large amount of deoxyribonucleic acid (DNA) production in mucous plugs [4,5]. Recombinant human deoxyribonuclease (rhDNase) extensively reduces the viscosity of mucous, transforming it from a viscous gel to a flowing liquid within minutes by hydrolysing extracellular DNA in mucous [6,7]. Inhaled form of rhDNase with nebulizer, has been well studied in cystic fibrosis (CF) [4-8]. Other than CF, in some studies rhDNase has been found effective in the treatment of respiratory syncytial virus bronchiolitis [3,9]. In addition, it was found effective in atelectasis of ventilated neonates [2,10] There has been limited data in premature newborn for the efficacy of rhDNase.

The aims of this study were to see the efficacy in atelectasis and clinical and radiological effectiveness of rhDNase in RDS newborns unresponsive to conventional therapy.

Material and Methods

Patients

Eight newborns (7 premature) with atelectasis in different parts of the lungs were participated in to the study. These patients had been already taken frequent aspiration, positioning, chest physiotherapy, endotracheal aspiration, medical treatment with N-acetylcysteine, 3% NaCl and salbutamol with nebulizer. rhDNase was given to all patients after these therapies. In addition, one patient received 3 times and the other patients received 2 times of surfactant with a dosage of 200 mg/kg [11] among the prematures.

The rhDNase treatment was explained to the parents and they signed a consent form in order to participate to the study. rhDNase was administered as a part of the medical treatment of the patients. However, this treatment was not

for the research. Because of this, approval from ethic committee was not needed.

Treatment

rhDNase (Germany Pulmosyme, Roche, Genentech Inc, San Francisco, CA, USA) was given to patients two times in a day (12 hours period) for 3 days with an amount of 2.5 mg each with nebulizer. The treatment protocol was based on previous study [3]. The outcomes of the treatment were retrospectively analyzed. Clinically, lung examination, respiration rate, oxygen needs for the patients and whether the patients were extubated or not were evaluated. Radiologic evaluation to all patients was made with chest radiograph. At their chest radiograph, partial or total atelectasis was evaluated.

The administration of rhDNase was associated especially with alteration in voice (e.g; hoarseness), pharyngitis and laryngitis. In addition, it was associated with rash, chest pain, and conjunctivitis. But no anaphylaxis was reported during rhDNase treatment [12]. The patients were observed for the possible side effects of rhDNase.

Results

Demographic and treatment characteristics of patients are shown in Table 1. Male & female ratio was 5/3 (1.66). Seven of 8 patients were premature newborns. The other patient, who was born in time, had diagnosis of hypoxic ischemic encephalopathy (HIE). The birth weight and gestational age of the patients ranged respectively from 500 g to 3000 g and 25 weeks to 41 weeks. When atelectasis developed, six of eight patients were mechanically ventilated. Our infants received a dosage of 2.5 mg rhDNase every 12 hours with nebulizer for 3 days. Mechanically ventilated patients received rhDNase by an apparatus connected to circulation of mechanical ventilator. Six of 8 patients showed almost complete improvement after the rhDNase treatment (Figure 1 and Figure 2). One patient (4th patient) who did not respond to the treatment had already an underlying HIE and complicated pneumonia in addition to being unresponsive to medical treatment. This patient died during the follow up. Other patient (3rd patient) gave partial response to treatment and general improvement was seen in aeration. Of 6 mechanically ventilated patients, 3 patients

Tablo 1. Demographic and treatment characteristic of patients

Gestational week (median, range)	29.4 (24-41)
Premature/mature	7/1
Birth weight (median, range)(grams)	1375 (500-3000)
Male/female	5/3
Mechanically ventilation/no ventilation	6/2
Age during rhDNase treatment (median, range) (days)	35.6 (13-70)
Duration of rhDNase treatment (median, range) (days)	3 (3)

**Figure 1.** Right side total atelectasis in 8th patient.**Figure 2.** Improvement of atelectasis in 3 days after rhDNase by nebulizer.

extubated in 3 days, one patient extubated after 9 days and 2 patients could not be extubated. Atelectasis relapsed in 6 patients. After second 3-day course of treatment by a nebulizer, recovery was seen in 3 days. And rhDNase was continued to these patients for 1 month. Five patients that had taken recurrent rhDNase treatment were reevaluated after 1 month of the treatment. Decrease at respiratory rate and oxygen need was seen in one patient. In this patient, in spite of not showing any development of new atelectasis, extubation could not be made. Respiratory rate and lung examination of other patients were normal and there was no new atelectasis. Characterization of atelectasis and treatment of patients are shown in table 2. The patients were evaluated for the possible side effects of rhDNase. But we didn't see any side effect resulted from rhDNase treatment during the study period.

Discussion

rhDNase (Dornase alfa), a recombinant enzyme, is a mucokinetic agent that degrades extracellular DNA. It can increase the clearance of mucous by increasing the effectiveness of cough, and by the thick secretions from

the airway walls [13]. It has been already well known and used for nearly 20 years and generally used in the treatment of patients with CF. In CF, it increases mucous clearance and regulates inflammatory process in the airway [14-16]. It was suggested that, apart from CF, rhDNase could be used in the management of pneumonia and mechanically ventilated patients with atelectasis unresponsive to conventional treatments [16].

In our study, 8 patients were analyzed retrospectively. At the study, 6 of 8 patients showed almost complete improvement after the rhDNase treatment and 4 patients recovered from the mechanical ventilation. Third patient gave partial response to treatment and general improvement in aeration was seen. This may be due to the underlying complicating pneumonia in this patient; because, rhDNase degrades the thick secretions from the airway and so increases the clearance of mucous. But it may not be effective for the treatment of the infection as clearance of mucous. In our study, atelectasis relapsed in 6 patients. We did not give rhDNase endotracheally as second regimen treatment. But rhDNase was administered to 5 of these 6 patients by a nebulizer and recovery was seen

Tablo 2. Diagnosis, characterization of atelectasis and treatment of patients

Patients	Diagnosis	Localization of atelectasis	Mechanical ventilation	Postnatal age at rhDNase treatment (day)	Duration of rhDNase treatment (day)	Extubation of patients after rhDNase treatment (day)	Recurrent atelectasis	Repeated rhDNase treatment
1 st patient	RDS, BPD	RUL	NO	47	3	-	NO	NO
2 nd patient	RDS, BPD	RUL	YES	26	3	Not extubated	YES	YES
3 rd patient	RDS, BPD, pneumonia	RLL, LLL	YES	44	3	3	YES	YES
4 th patient	HIE, pneumonia	RUL	YES	36	3	Not extubated	YES	NO
5 th patient	RDS, BPD	RUL	YES	13	3	2	YES	YES
6 th patient	RDS	Total right lung	YES	21	3	9	YES	YES
7 th patient	RDS, esophageal atresia RDS	RUL	YES	70	3	3	YES	YES
8 th patient	RDS, ASD	Total right lung	NO	28	3	-	NO	NO

ASD: atrial septal defect; RDS: respiratory distress syndrome; BPD: bronchopulmonary dysplasia; HIE: hypoxic ischemic encephalopathy; RUL: right upper lung; RLL: right lower lung, LLL: left lower lung

in 3 days. Because patient with HIE did not benefit from medication with rhDNase, it was not administered again to this patient. rhDNase was continued to other patients for 1 month against the possibility of re-occurrence of atelectasis. After 1 month, patients were evaluated and none of them had new atelectasis.

In one study, atelectasis developed after severe RSV bronchiolitis in 5 infants [3]. rhDNase with nebulizer (2.5 mg twice daily) was administered to these infants for two days and after administration of rhDNase, all infants showed clinical and radiological improvement after the first dose of rhDNase. Two patients recovered from ventilation after the treatment, while 3 other patients showed dramatic improvement. In the study of Fedakar et al [17], 12 prematures and 10 term newborns received rhDNase with a dose of 1 mg/m² twice daily for 3 days. They observed a clinical and radiologic improvement of atelectasis in 18 patients. Endotracheal and nebulized rhDNase treatment was administered to 4 patients in whom atelectasis was relapsed. Improvement of atelectasis was reported in these patients also. They did not see any side effects due to treatment like our study. Erdeve et al [2], gave nebulized rhDNase therapy at a dose of 1.25 mg over a 15-minute period, twice a day (2 hours between the doses) for up to 3 days to newborns (10 preterms), who did not respond to

conventional methods. Two patients who did not respond to this treatment received an additional single dose of the rhDNase endotracheally and showed clinical and radiological improvement. In our study, two patients did not mechanically ventilated and had complete recovery for atelectasis after treatment. Of 6 mechanically ventilated patients 4 patients recovered from the mechanical ventilation. One patient gave partial response to treatment and general improvement in aeration was seen. In our study, atelectasis relapsed in 6 patients. In the study of Fedakar et al [17] and Erdeve et al [2], rhDNase was administered endotracheally in the second regimen. But, we gave rhDNase with nebulizer again to 5 of these 6 patients. And recovery was seen in 3 days. rhDNase was continued to these patients for 1 month against the possibility of re-occurrence of atelectasis. After 1 month, patients were evaluated and none of the patients had new atelectasis. El Hassan et al [18] also reported the effectiveness of rhDNase in 3 premature infants like our study.

Riethmueller et al. [19] reported that in infants who received rhDNase the incidence of atelectasis, median ventilation time and median length of stay in intensive care unit were lower than placebo group, but re-intubation rates did not change. In our study six of 8 patients showed almost complete improvement after the rhDNase treatment. In addition, of 6

mechanically ventilated patients, 4 patients could be extubated.

According to results of our study, seven patients had beneficial effect from rhDNase treatment, especially if there was not any underlying disease. Voice alteration and rash were reported as the mild side effects of rhDNase in CF patients [20]. In addition, the administration of rhDNase was associated with alteration in pharyngitis, laryngitis, chest pain, and conjunctivitis [12]. But in our study, rhDNase was administered to patients with no clear side effect.

In a study, no statistical difference was found between hypertonic saline, normal saline, and dornase alpha in the treatment of atelectasis [21]. However, in our study, all patients were already taken hypertonic saline treatment which is a part of traditional treatment and their atelectasis did not get better via this treatment. During hypertonic saline treatment, rhDNase treatment was also begun. Hence, comparison could not be made.

Limitations of the study: Comparison should be made with hypertonic saline treatment. But, when rhDNase treatment was begun, the patients were already taken hypertonic saline treatment. So we couldn't compare them with each other. In addition, long term following of the patients is also important in terms of finding out side effects. Another issue can be thought as the insufficient number of the patients; so, working with more patients and control group are needed in order to provide more successful outcomes in this work. Moreover, if the patients could be followed prospectively rather than retrospectively, the possible adverse effect could be determined easier.

We suggest that rhDNase may be administered as an alternative treatment to the newborn infants with atelectasis in their lung; especially, if there was not any underlying disease and if they did not respond to conventional treatment for atelectasis.

Conflict of interest: The authors declared no conflict of interest.

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