Practice of Intratracheal and Inhaled Recombinant Human Deoxyribonuclease (rhDNase) Therapy in Neonates with Persistent Atelectasis: A Rescue Treatment

Persistan Atelektazili Yenidoğanlarda İntratrakeal ve İnhale Rekombinan İnsan Deoksiribonükleaz (rhDNase) Uygulaması: Bir Kurtarma Tedavisi

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ABSTRACT Objective: Atelectasis increases the risk of secondary pulmonary infections related with prolonged artificial ventilation. Therefore, it requires early and aggressive treatment in newborns cared in neonatal intensive care units (NICUs). Current treatment of atelectasis consists of certain conventional modalities. However, there is still no evidence-based, "gold standard" treatment. Use of recombinant human deoxyribonuclease (rhDNase) is a new concept in NICUs. In this study, we aimed to compare and evaluate the clinical and radiological changes in infants who received nebulized or intratracheal rhDNase for persistent atelectasis unresponsive to conventional treatment options. **Material and Methods:** This study was conducted in 23 newborns hospitalized at the NICU of Dr. Behcet Uz Children's Hospital. Twelve intubated patients received 1.25 mg rhDNase mixed with 1:1 0.9% saline intratracheally, whereas 11 non-intubated patients received the drug via a jet nebulizer. A second dose was administered 4 hours after the initial dose. Chest physiotherapy and tracheal aspiration was performed 1 hour after the second dose. The same protocol was repeated on the second day. Clinical and radiological responses were evaluated separately. **Results:** Positive radiological and clinical responses to rhDNase and recurrence of atelectasis in the whole study group were 78.3%, 56.3% and 16.7% respectively. Nebulized route was more successful than the intratracheal route. Response to rhDNase was better in cases with upper lung lobe involvement. **Conclusion:** Both nebulized and intratracheal rhDNase administrations are successful without any adverse reactions for the treatment of persistent atelectasis, especially in neonates with viscous secretions and pneumonia with upper lobe atelectasis.

Key Words: Pulmonary atelectasis; infant, newborn; DNASE1 protein, human; mucus

ÖZET Amaç: Atelektazi, uzamış mekanik ventilasyona neden olarak ikincil akciğer enfeksiyonu riskini arttırır. Bu nedenle yenidoğan yoğun bakım ünitelerinde (YYBÜ) yatmakta olan bebeklerde atelektazinin erken ve agresif tedavisi zorunludur. Atelektazinin güncel tedavisi bazı konvansiyonel yöntemlerden oluşmaktadır. Ancak halen kanıta dayalı "altın-standart" bir yöntem bulunmamaktadır. YYBÜ'de rekombinan insan deoksiribonükleazının (rhDNase) kullanımı yeni bir uygulamadır. Bu çalışmada konvansiyonel tedavi seçeneklerine dirençli persistan atelektazisi olan yenidoğanlarda, nebulize ve intratrakeal yollardan uygulanan rhDNase tedavisini kıyaslamayı ve klinik ve radyolojik değişiklikleri değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Bu çalışmaya Dr. Behçet Uz Çocuk Hastanesi YYBÜ'de izlenen 23 yenidoğan dahil edildi. Entübe olarak izlenen 12 hastaya, 1,25 mg rhDNase 1:1 %0,9 salinle karıştırıldıktan sonra, intratrakeal yoldan; entübe olmayan 11 hastaya ise nebulize yoldan uygulandı. İlk dozdan 4 saat sonra ikinci doz verildi. İkinci dozdan 1 saat sonra göğüs fizyoterapisi ve trakeal aspirasyon yapıldı. İkinci gün aynı protokol tekrarlandı. Klinik ve radyolojik yanıtlar ayrı ayrı değerlendirildi. **Bulgular:** Tüm çalışma grubu ele alındığında, rhDNase tedavisine alınan olumlu radyolojik ve klinik yanıt ile atelektazinin tekrarlama oranları sırasıyla %78,3, %56,3 ve %16,7 olarak değerlendirildi. Nebülize uygulama yolu intratrakeal yoldan daha başarılı bulundu. rhDNase tedavisine yanıtın üst akciğer loblarının tutulumunda daha iyi olduğu görüldü. **Sonuç:** Özellikle yapışkan salgıları, pnömonisi ve üst akciğer loblarında persistan atelektazisi olan yenidoğanlarda rhDNase'ın hem nebulize, hem de intratrakeal uygulamaları başarılı bulunmuş olup, herhangi bir yan etkiye rastlanmamıştır.

Anahtar Kelimeler: Akciğer atelektazisi; bebek, yenidoğan; DNASE1 protein, insan; mukus

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Airway obstruction and atelectasis due to excessive or thick pulmonary secretions and mucus-plugging are common clinical challenges in newborns cared for in neonatal intensive care units (NICUs). The presence of mucus-plugging and abundant thickened pulmonary secretions are risk factors for pulmonary infections and for prolonged artificial ventilation; therefore, atelectasis in newborns requires early and aggressive treatment.[1] However, the efficacy and safety of conventional treatment modalities, such as frequent aspiration and positioning, chest physiotherapy, blind bronchial irrigation with NaCl 0.9%, inhalation of hypertonic saline (NaCl 3%), N-acetylcysteine (NAS), bronchodilators and steroids, have not been well demonstrated.[2] Recombinant human DNase (rhDNase) has proven to be an effective treatment to reduce sputum viscoelasticity, to open airways and to improve lung function in cystic fibrosis (CF), by fragmenting the extracellular DNA derived from degenerating leukocytes and epithelial debris.[3-6] Several case reports have also described the beneficial effects of rhDNase in other respiratory disorders in children.[7-9] The use of rhDNase for the treatment of atelectasis, in which it is intended to liquefy the mucus when conventional therapies fail, is a new concept in NICUs.[10-12] In this study, we aimed to compare and evaluate the clinical and radiological responses in neonates who received nebulized and intratracheal (IT) rhDNase treatment for persistent atelectasis that was unresponsive to conventional treatment options.

MATERIAL AND METHODS

This study was conducted between January 2007 and November 2008 in the NICU of the Dr. Behcet Uz Children's Hospital, in 23 term and preterm neonates with atelectasis on chest X-ray that was unresponsive to conventional treatment options.

Thirteen out of 23 patients had an experience of mechanical ventilation for various periods of time during their NICU follow-up. Ten infants were never intubated, but they received noninvasive ventilation for different durations. One infant who had been intubated prior to the treatment, was extubated during the treatment. In the course of the study, the number of patients who were mechanically ventilated was 12, and they received IT rhDNase (Dornase alpha 1 mg= 1 ml inhalation solution, 2.5 ml). On the other hand non-ventilated 11 infants received the nebulized form of the drug.

Gender, gestational age, birth weight, primary diagnosis, antibiotic use, the location and the extent of atelectasis, baseline C-reactive protein (CRP) level, mechanical ventilation (MV) requirement, postnatal age during treatment, treatment route, clinical and radiological responses, side effects of treatment and recurrence of atelectasis were recorded. The diagnosis of respiratory distress syndrome (RDS) was based on a combination of the clinical features (grunting respiration, retraction, nasal flaring, cyanosis, and an increased oxygen requirement), evidence of prematurity, the exclusion of other causes of respiratory distress, a characteristic radiographic appearance (diffuse reticulogranular pattern, yielding the classic ground-glass appearance in both lung fields with superimposed air bronchograms) and onset of symptoms shortly after birth.[13] The diagnosis of neonatal sepsis was based on the Tollner Scoring System and/or CRP >1 mg/dL and/or a positive blood culture.[14] The ratio of the duration of mechanical ventilation (MVt) to postnatal age (PNA) was calculated (MVt/PNA).

The locations of atelectatic lesions were classified according to lung segments as upper right zone, upper left zone, middle right zone, middle left zone, lower right zone, lower left zone, total right lung, total left lung or diffuse atelectasis. However, to avoid statistical failure due to an insufficient number of subjects in each group, this classification was simplified to lesions in the upper lobe or lesions in other locations.

In intubated patients, 1.25 mg Dornase alpha mixed with 1:1 0.9% saline was infused slowly in the endotracheal tube (ETT) via a feeding tube. The infant was then reventilated with his/her previous settings. The same procedure was repeated 4 hours after the initial dose. In non-intubated patients, 1.25 mg Pulmozyme mixed with 1:1 0.9% saline was placed in a chamber, and was applied via a mask through jet nebulizer (OMRON CompAIR

Elite NE-C30-E], Omron Corporation of Kyoto, Japan). Moisturized oxygen (4-6 L/min) was also administered during and after nebulization. The same procedure was repeated 4 hours after the initial dose. Chest physiotherapy and standard tracheal aspiration were performed 1 hour after the second drug dose, for both treatment routes. The same treatment protocol was repeated on the second day. Blood gas analysis and chest X-rays were performed prior to the initial treatment and 1 hour after the tracheal aspiration on the second day. Treatment responses were evaluated separately as "clinical" and "radiological" responses.

For patients on mechanical ventilation, a "positive clinical response" was defined at the end of the second day as one of the following: (1) ≥2 cm H_2O reductions in PIP (peak inspiratory pressure) and PEEP (positive end expiratory pressure) values when compared to baseline settings; (2) a ≥20% reduction in the FiO_2 (inspired fraction of oxygen) requirement when compared to baseline values; (3) a significant decrease (≥15 mm Hg) in $PaCO_2$ values when compared to baseline blood gas results; or (4) an improvement in oxygenation (≥20 mm Hg increase in PaO_2 when compared to baseline blood gas results). If the patient was not on mechanical ventilation, a "positive clinical response" at the end of the second day was defined as one of the following: (1) a ≥20% reduction in the inhaled oxygen requirement; (2) a ≥20% reduction in breath rate; (3) a significant decrease (≥15 mm Hg) in $PaCO_2$ values when compared to baseline blood gas results; or (4) an improvement in oxygenation (≥20 mm Hg increase in PaO_2 when compared to baseline blood gas results). Infants in either patient group not exhibiting any of these changes were assessed as having "no clinical response".[11,12]

Radiological responses were evaluated by the same radiologist. "Complete radiological recovery" was defined as complete recruitment of the previous atelectatic lesion, and "no radiological response" was defined as partial or no improvement in the previous lesion.

Statistical analysis was performed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Mean ± standard deviation or median (minimum-maximum) values were given for continuous variables. Categorical variables were expressed as frequency and related percentage values. Comparison of continuous variables between the study groups were performed with Mann Whitney test. On the other hand, Fisher's exact test was preferred for the analysis of categorical variables between the groups. The variables affecting radiological response were studied with logistic regression analysis. A p value <0.05 was considered to be statistically significant.

The authors confirm that this study was undertaken in compliance with the guidelines of the Declaration of Helsinki, it was approved by the ethics committee of the Dr. Behcet Uz Children's Hospital and the parents gave their informed consent after receiving detailed explanations about the treatment protocols.

The authors declare that they have no conflicts of interest and any financial agreements with pharmaceutical or biomedical firms whose products are pertinent to the subject matter dealt within the manuscript.

RESULTS

Demographical features (gender, mean gestational age, mean birth weight) are presented in Table 1. Out of the entire group, 73.9% (n=17) of the patients were preterm infants, whereas 26.1% (n=6) were full-term infants. The distributions of the patients, according to their primary diagnoses and the locations of their atelectatic lesions are presented in Tables 2 and 3. When the entire study group was considered, the most frequent primary diagnosis was RDS (60.9%), and the most frequently affected lung segment was the upper right zone (52.2%). The overall upper lobe involvement proportion was 56.5% (n=13). No statistically significant relationship could be demonstrated between the gestational age and the location of the atelectatic lesion (p=0.639; for upper right lobe involvement median=30 weeks, min=26 weeks, max=40 weeks; for other lung lobes median=35 weeks, min=27 weeks, max=40 weeks). Similarly, there was not a significant relationship between the birth weight and the location of the atelectatic lesion (p=0.114)

TABLE 1: Demographical features of patients.

Variable	Values
Gender (female/male)	11 (47.8)/12 (52.2)
Maturity (premature/mature)	17 (73.9)/6 (26.1)
Gestational age*	32.4±4.9
Birthweight**	1415 (780-4100)

* Weeks; ** Grams.
Values are expressed as mean±standard deviation, median (min-max) or n (%).

TABLE 2: Distribution of patients according to primary diagnosis.

Diagnosis	n (%)
RDS	14 (60.9)
RDS + BPD	2 (8.7)
Sepsis	1 (4.3)
Pnx	1 (4.3)
IUBP	3 (13)
Asphyxia	2 (8.7)
Total	**23 (100)**

RDS: Respiratory distress syndrome; BPD: Bronchopulmonary dysplasia; Pnx: Pneumothorax; IUBP: Intrauterine bronchopneumonia.
Values are expressed as numbers and percentages.

TABLE 3: Location of the atelectatic lesion on chest X-ray.

Location	n (%)
Upper right zone	12 (52.2)
Upper left zone	1 (4.3)
Middle right zone	2 (8.7)
Lower right zone	3 (13)
Total right lung	2 (8.7)
Total left lung	1 (4.3)
Diffuse lung segments	2 (8.7)
Total	**23 (100)**

Values are expressed as numbers and percentages.

In the "positive clinical response" group, 76.9% of the patients had atelectasis in the upper right zone. In contrast, in the "no clinical response" group, 80% of the atelectatic lesions were distributed equally in the upper right zone (20%), middle right zone (20%), lower right zone (20%) and in diffuse lung segments (20%). In the "complete radiological recovery" group, 66.6% of the patients had atelectasis in the upper right zone. However, the atelectatic lesions in the "no radiological response" group were distributed in the upper right zone (20%), middle right zone (20%), lower right zone (20%) and in diffuse lung segments (40%). The relationship between the clinical response and the location of the atelectatic lesion was statistically significant (p=0.040) (Table 4). In contrast, the relationship between the radiological response and the location of the atelectatic lesion was statistically insignificant (p=0.125) (Table 4).

MV requirement, CRP positivity, antibiotic use, treatment route (ETT or nebulizer) and the location of the atelectatic lesion in association with clinical response and radiological response are presented in Table 4. The duration of MV (MVt), MVt/PNA ratio, postnatal age during treatment in association with clinical response and radiological response are presented in Table 5. Although the statistical relationship of radiological response with gender, treatment route, MV requirement and clinical response ($p<0.05$) were significant, the opposite was true for gestational age, birth weight, duration of MV (MVt), MVt/PNA ratio, antibiotic use, CRP positivity and postnatal age during treatment ($p>0.05$) (Tables 4, 5). The relationship between the clinical response and all other variables were statistically insignificant except for the location of the atelectatic lesion (Table 4).

Within the "complete radiological recovery" group, recurrence of atelectasis was observed in 3 patients (16.7%). None of the patients developed any drug-associated side effects. No significant variables affecting radiological response could be detected in the logistic regression analysis.

DISCUSSION

Atelectasis, described as a reversible loss of the aeration of the lung, is a common complication in mechanically ventilated neonates. The developing lung is particularly predisposed to atelectasis once airway obstruction develops.[15-17] In neonates, the airways are smaller and more collapsible, and the chest wall is more compliant as compared to term infants. Surfactant deficiency or dysfunction, which is present in most of the pulmonary problems of newborns,

TABLE 4: Relationship of clinical response and radiological response with other variables.

		Radiological Response			Clinical Response		
		Yes (n/%)	No (n/%)	p	Yes (n/%)	No (n/%)	p
Variable		(18/78.3)	(5/21.7)	(RR)	(13/56.5)	(10/43.5)	(CR)
MV	Yes	8 (34.8)	5 (21.7)	**0.046**	8 (34.8)	5 (21.7)	0.685
	No	10 (43.5)	0 (0)		5 (21.7)	5 (21.7)	
CRP (+)	Yes	7 (30.4)	1 (4.3)	0.621	7 (30.4)	1 (4.3)	0.074
	No	11 (47.8)	4 (17.4)		6 (26.1)	9 (39.1)	
AB use	Yes	16 (69.6)	5 (21.7)	1	12 (52.2)	9 (39.1)	0.322
	No	2 (8.7)	0 (0)		1 (4.3)	1 (4.3)	
RA	IT	7 (30.4)	5 (21.7)	**0.037**	7 (30.4)	5 (21.7)	1
	Neb	11 (47.8)	0 (0)		6 (26.1)	5 (21.7)	
LAL	UR	12 (52.2)	1 (4.3)	0.127	10 (43.5)	3 (13)	**0.040**
	Other	6 (26.1)	4 (17.4)		3 (13)	7 (30.5)	

MV: Mechanical ventilation; CRP (+): C-reactive protein positivity; AB use: Antibiotic use; RA: Route of administration; LAL: The location of the atelectatic lesion; IT: Intratracheal; UR: Upper right zone; RR: Radiologic response; CR: Clinical response.

causes increased alveolar surface tension, with consequent diffuse atelectasis. In addition, neonates, and especially preterm infants, have insufficient ability to clear thick and purulent airway secretions due to a small airway caliber and ineffective cough mechanisms.[11] Due to all of these precipitating factors, some airways become partially or completely occluded, leading to air trapping and hyperinflation or atelectasis in newborns.[15]

Atelectasis can increase mortality and morbidity in the NICU due to prolonged MV, secondary pulmonary infections and longer hospitalization durations.[9,12] MV-associated tissue edema, increased secretion of mucus, impaired natural ciliary activity, decreased clearance of secretions and necrosis of the respiratory epithelium due to inflammatory responses can result in disruption of the normal airflow.[2,11] Furthermore, damage to the respiratory mucosa facilitates bacterial colonization and precipitates pooling of contaminated secretions, resulting in aspiration of infected material into distal airways.[9,11] Due to the lysis of inflammatory cells, significant amounts of DNA accumulate in mucus plugs. DNA increases the viscosity and adhesiveness of lung secretions.[18] In addition, restrictive fluid management and diuretic therapy can result in the thickening and retention of tracheal and bronchial secretions.[18] Ultimately, total lung function decreases, and the infant becomes susceptible to recurrent respiratory infections.[8]

TABLE 5: Relationship of clinical response and radiological response with mechanical ventilation.

			n	Median (min-max)	p
Radiological Response	Yes	MVt (days)	18	8 (1-100)	0.073
	No		5	17 (9-121)	
	Yes	MVt/PNA	18	0.825 (0.16-1)	0.070
	No		5	1 (1-1)	
	Yes	AT (days)	18	9.5 (5-101)	0.279
	No		5	17 (9-121)	
Clinical Response	Yes	MVt (days)	13	10 (2-100)	0.437
	No		10	8 (1-121)	
	Yes	MVt/PNA	13	1 (0.28-1)	0.547
	No		10	0.925 (0.16-1)	
	Yes	AT (days)	13	10 (5-101)	0.828
	No		10	11.5 (5-121)	

MVt: Duration of mechanical ventilation; MVt/PNA: The ratio of MVt to postnatal age; AT: Postnatal ageduring treatment.

The present study group consisted of both term and preterm infants with primary or secondary pulmonary diseases (RDS, bronchopulmonary dysplasia, intrauterine pneumonia or pneumothorax) and atelectasis. Of the entire group, 60% of the patients required MV, with a median duration of 20 days.

The treatment of atelectasis is based primarily on the reduction or complete recruitment of non-ventilated lung segments and the prevention of sec-

ondary pulmonary infections.[8] The current treatment of atelectasis in pediatric cases consists of increasing ventilation parameters (PEEP, PIP and FiO_2), regular physiotherapy, positioning, secretolysis (N-acetyl cystein, ambroxol), inhaled bronchodilators, antibiotic treatment if necessary, intermittent tracheal lavage with saline or secretolytics via ETT and fiberoptic bronchoscopy (FOB).[19] However, there is still no evidence-based "gold standard" treatment.[8] In a recent study, FOB identified the etiology in 2/3 of 56 infants with persistent atelectasis, of whom 64% were younger than 6 months of age, with the youngest patient being 24 days old. Mucus plugs occluding airways were removed successfully with repeated suction and saline wash in 16 patients (28.5%).[20] In our study, the patients had received but failed to respond to any of the above-mentioned conventional treatments. We could not perform FOB because it is quite an invasive method for neonates.

Recently, nebulized or direct tracheal application of rhDNase-a drug primarily used in CF patients with highly viscous secretions-has been shown to reduce the viscoelastic properties of purulent airway secretions by breaking down the highly polymerized DNA that is also present in non-CF patient groups.[8,9] rhDNase was also shown in the Pulmozyme Early Intervention Trial (PEIT) study to improve mucus clearance and reduce pulmonary infection rates in sedated and ventilated patients.[21] In CF patients older than 5 years of age, significant improvement in FEV_1 (forced expiratory volume in 1 second) was not associated with decreased cellular markers of airway inflammation after rhDNase therapy.[3] However, another study showed a significant reduction in the inflammatory parameters of leukocyte count, DNA content and IL-8 concentrations.[8] rhDNase, administered in a dose of 2.5 mg bid, did not reduce the duration of hospital stays or oxygen supplementation in <12-month-old infants who were hospitalized for RSV (respiratory syncytial virus) bronchiolitis. One probable reason for this finding might have been that rhDNase accumulates more in the central airways, while the airway obstruction in RSV is peripheral.[18]

Thus far, the effects of rhDNase have not been proven in neonates who are unresponsive to conventional treatment modalities for atelectasis due to viscous and purulent secretions. There have also been no randomized controlled studies to determine a safe and effective route for the administration or the recommended dose and duration of therapy in neonates. In the limited number of published studies, El Hassan et al. successfully administered the drug for 3 days in 3 preterm infants via nebulization (1.25 mg) or IT route (1 mg/m^2).[1] In a study of Erdeve et al., complete recovery was observed in a term neonate with total left lung atelectasis after administration of 1.25 mg nebulized rhDNase for 3 days.[22] In another study conducted by the same researchers, neonates with severe atelectasis received 1.2 mg of rhDNase bid by nebulization for 3 days.[11] Non-responders were administered an extra single 1.25 ml IT dose, and atelectasis then resolved in these patients. Dilmen et al. treated patients until atelectasis resolved.[12] Because a longer duration of treatment is associated with high treatment costs, we preferred a 1.25 mg dose bid for 2 days via nebulizer or ETT.

In the present study, of the patients without clinical responses, 90% were CRP-negative although it could not be confirmed statistically. This result possibly indicates that patients with pneumonia and with purulent secretions responded better to rhDNase treatment, because in the presence of pneumonia, sticky mucus plugs with higher polyamine DNA content are expected to respond to rhDNase administration. In contrast, the mucus in pneumonia, which is partially liquefied by treatment, is more mobilized, and it may thicken again before being fully dispersed, as immediate and frequent aspiration has not been administered.[2,9] The use of antibiotics was not found to be correlated with clinical response, most likely because nearly all of the patients (91.3%) were on antibiotics due to several clinical problems other than intrauterine or nosocomial pneumonia.

Treatment age and birth weight might have changed responses to treatment with regard to airway diameter. However, demographic characteristics were not correlated with clinical or radiological

response or with recurrence of atelectasis in our patients. The significantly better radiological response in male infants was considered to be coincidental.

Studies do not exist comparing the use of the drug via nebulization or via an IT route. Kupeli et al. reported that in nebulized administration, the plug was first liquefied as a response to the drug, and then, a large amount of secretion created new atelectatic sites despite frequent aspiration.[10] In contrast, after direct IT instillation, the mucus was most likely rapidly mobilized, causing increased airway obstruction and a ventilation/perfusion (V/P) imbalance. Therefore, slow IT administration, in lower doses and volumes, might be more appropriate in ventilated infants requiring rhDNase treatment.[9]

In our study, we observed significantly better radiological responses in patients who received nebulized rhDNase, which might also have been affected by the fact that the infants who were given IT rhDNase had more severe pulmonary disease requiring MV. Most patients with poor radiologic response required MV expressing a significant statistical relationship. Clinical response and the recurrence of atelectasis were unrelated to the presence and duration of MV and to the MVt/PNA ratio. We can conclude that, even in patients without clinical improvement, atelectatic lesions resolved, as observed in the radiological examinations.

In our study, patients with upper right lobe atelectasis benefited from the treatment more than the patients with atelectasis at other lung sites. This effect might be related to the drug reaching the upper bronchial tree first, as postulated by Durward et al., thus explaining the failure in RSV patients due to the accumulation of the drug in the central bronchi, thereby causing less drug delivery to the peripheral lung segments.[23] In previous reports, in 1 of 3 patients in El- Hassan et al.'s study and in 2 of 12 patients in Erdeve et al.'s study, atelectasis recurred, and the patients required additional doses.[1,11] Kupeli et al. stated that recurrence was frequent despite effective drug administration.[10] In our study, the recurrence rate was only 16.7% in rhDNase responders.

The reported side effects of rhDNase are rare and mild in most cases, and they resolve spontaneously. They include chest pain, fever, vocal changes, laryngitis, pharyngitis, dyspepsia, facial edema, conjunctivitis, rhinitis, impaired liver function tests, rashes, hives, and in less than 5% of patients, antibody formation.[10,24] Most of these findings cannot be fully evaluated in newborn infants. Kristensen reported increased pulmonary exacerbation and impairment of pulmonary function tests in adults with idiopathic bronchiectasis.[25] Rochat et al. demonstrated a dose-dependent increase in damaged airway protease activity.[26] The clinical significance of this finding is not known, but it might indicate a potential hazard in preterm infants. Similar to Erdeve et al., we did not observe any remarkable side effects in our group, which mostly consisted of preterm infants.[10]

Recent randomized controlled trials with different agents for atelectasis treatment have been controversial. Dilmen et al. had better clinical and radiological results with nebulized rhDNase compared to 3% HS.[12] Although it is more expensive, we believe that treatment with rhDNase is a better option, with the potential to shorten the duration of MV. In ventilated 87 neonates with atelectasis, rhDNase monotherapy was superior to 7% HS, and a combination therapy of rhDNase with saline decreased both cost and treatment duration compared to either agent as a monotherapy.[27] Similarly, MacKinnon et al. showed clinical improvement after administration of endotracheal rhDNase in a subgroup of ventilated neonates with severe end-stage respiratory failure and atelectasis.[28]

In conclusion, the efficacy and safety of rhDNase, administered via ETT or nebulizer, were confirmed in our series of 23 term and preterm infants. The rates of radiological response, clinical response and recurrence of atelectasis were 78.3%, 56.3%, and 16.7%, respectively; thus, we encourage clinicians to apply this new treatment. The nebulized route used in non-ventilated patients was more successful than IT treatment in patients who were on MV. Although statistical analysis supports this data only for good radiologic responders but not for clinical responders, this finding might be related to the oblig-

atory choice of IT route for ventilated infants. The response to rhDNase is better in cases with atelectasis in the upper right lobe, most likely due to better drug delivery. Recurrence was not frequent, and no variable could predict the recurrence of atelectasis.

The major limitation of our study was the non-randomized design comparing the IT and nebulized routes of drug administration in ventilated and non-ventilated infants. Other important limitations were that the treatment groups differed in terms of respiratory support and the study was an open ended observational study. In this respect, we conclude that the study results might have been affected from above mentioned factors. On the other hand, the strength of this study was that it was the first study assessing the success of short-term therapy administered via different routes and evaluating the variables affecting clinical and radiological responses.

Pharmacological studies for the dosing and duration of the rhDNase, studies of combination therapies, studies evaluating tracheal aspiration to demonstrate inflammatory responses and local side effects, and reports differentiating etiological problems might be future areas of investigation.

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