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Recombinant Human Deoxyribonuclease Improves Atelectasis in Mechanically Ventilated Children with Cardiac Disease

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Abstract

Objective—To investigate if a mucolytic agent, recombinant human deoxyribonuclease (rhDNase), improves atelectasis in children with cardiac illness requiring mechanical ventilation.

Design—A retrospective cohort study on consecutive patients receiving short-term (≤ 14 days) rhDNase therapy for atelectasis in the cardiac intensive care unit from January 2005 through February 2007 was carried out. Data relating to patient characteristics, gas exchange, ventilatory parameters and chest radiographs was collected and analyzed. The effectiveness of rhDNase therapy in the presence of neutrophils and/or bacteria in the pre-rhDNase therapy tracheal aspirates was also investigated.

Results—rhDNase was effective in significantly improving established atelectasis without any major changes in gas exchange and ventilatory parameters. Therapeutic effect of rhDNase is most effective in ameliorating atelectasis in the lungs within 10 doses. rhDNase was more effective in improving chest radiographic atelectasis score in patients who had $>$ moderate amounts PMN (p value= 0.0008), or bacteria (p value=0.007) or both (p value =0.004) present in their pre-rhDNase therapy trachea aspirate. No adverse effects were seen with rhDNase administration in the study cohort.

Conclusions—rhDNase can be safely and effectively used to improve atelectasis in mechanically ventilated children with cardiac disease especially in the presence of bacteria and/or moderate amounts of PMN in the pre-rhDNase therapy tracheal aspirate.

INTRODUCTION

Atelectasis, described as a reversible loss of aerated lung is a common pulmonary complication among children requiring mechanical ventilation. Anywhere from 10% to 54% of children while on mechanical ventilation develop atelectasis.^{1–6} The development of atelectasis is associated with several pathophysiologic effects, which includes decreased compliance, impairment of gas exchange, increased pulmonary vascular resistance and the

development of lung injury.⁷ Its presence increases morbidity, as the duration of mechanical ventilation, and hospital length of stay are prolonged.^{6,7}

Atelectasis in part occurs as a result of excess amount of mucus secretion and or retention of thickened mucus.⁷⁻⁹ The tenacious properties of airway secretions depends primarily on the presence of highly polymerized, polyanionic DNA, contributed mostly from degenerating polymorphonuclear leukocytes however hydration status may also influence this property.⁹⁻¹⁰ Thick and viscous mucus secretions plug the airway lumen, causing airway occlusion and atelectasis which results in disrupted airflow, ventilation perfusion mismatch and impaired gas exchange.

Due to the morbidity associated with persistent pulmonary atelectasis, it requires aggressive treatment. However, the efficacy and safety of treatment modalities such as inhaled bronchodilators, steroids, chest physiotherapy, nebulized sodium chloride (NaCl 0.9% and 3%), sodium bicarbonate and respiratory therapy for treatment of atelectasis in children has not been well demonstrated.⁸ A mucolytic agent, recombinant human deoxyribonuclease (rhDNase) may directly treat the pathophysiology of atelectasis by liquefying thick mucous plugs and improve atelectasis in patients with acute respiratory failure. rhDNase hydrolyzes extracellular DNA in sputum, transforms it from a viscous gel to a flowing liquid which can be removed by chest physiotherapy and airway suctioning.¹¹ rhDNase, currently used extensively in children with cystic fibrosis (CF) and in some patients with other respiratory disorders¹⁶⁻²² breaks down thick secretions within the airways¹²⁻¹³ and allows for better air flow within the lungs. This therapy by a similar mechanism is likely to liquefy the thick mucous secretions in the lungs of patients with cardiac illness and improve atelectasis.

Atelectasis is a common problem after cardiac surgery requiring cardiopulmonary bypass (CPB). Furthermore, the CPB-associated atelectasis accounted for most of the marked post-CPB increase in shunt and hypoxemia.¹⁴ Among mechanically ventilated children with cardiac disease atelectasis is also a common clinical finding.¹⁵ In these patients rhDNase has been shown to shorten duration of mechanical ventilation time when used prophylactically from the first day of intubation, thus decreasing median ventilation time and intensive care unit (ICU) length of stay.¹⁵ However, it is not known whether rhDNase is effective in reversing established atelectasis in this population. We hypothesized that rhDNase is effective in reversing established atelectasis in mechanically ventilated patients with cardiac disease. We further hypothesized that rhDNase is more effective when PMN and/ or bacterial is present in the airway prior to starting rhDNase therapy.

MATERIALS AND METHODS

Study subjects

After Institutional Review Board approval, this retrospective study included consecutive patients admitted to the cardiac intensive care unit (CICU) who received ≤ 2 weeks of rhDNase therapy for established atelectasis at Arkansas Children's Hospital, Little Rock, from January 2005 through February 2007. Patients for this study were identified through the computerized pharmacy records and the cardiovascular surgical database. We chose two weeks as a cut-off for our inclusion criteria as we were looking to investigate the efficacy of short-term rhDNase therapy, *a priori* defined as ≤ 2 weeks. Patients who received > 2 weeks of rhDNase therapy and those with cystic fibrosis, prematurity, chronic lung disease, and anatomical airway abnormalities were excluded from this study.

Method

The medical records and the chest radiograph of 38 eligible subjects were reviewed. Demographic data collected included age, gender, and underlying clinical diagnosis. The

clinical parameters analyzed were heart rate (HR), respiratory rate (RR), arterial P_aCO_2 , inspired oxygen concentration (FiO_2), peak inspiratory pressure, mean airway pressure, before and within 2 hour following administration of each dose of rhDNase. The presence of any bacteria and/or polymorphonuclear neutrophils (PMN) in the tracheal aspirate prior to the administration of the first dose of rhDNase was documented. The amount of PMN in the tracheal aspirate was graded as none, few, moderate, numerous by independent technicians blinded to the study variables. Atelectasis on chest x-ray, before and within 24 hours of treatment with rhDNase, was quantified using a chest x-ray score. Data relating to the type and frequency chest physiotherapy (intermittent positive-pressure ventilation, mechanical percussion / vibratory techniques) used on these patients after rhDNase was administered were also recorded. Cardio-respiratory endpoints considered were change in clinical parameters (HR, RR, PCO_2 , and FiO_2) before and within 2 hours after the first dose of rhDNase, and the chest x-ray score before and within 24 hours after the first dose of rhDNase. All parameters except chest x-ray changes were compared before and within 2 hours following treatment with rhDNase.

rhDNase therapy was administered when new onset atelectasis persisted atleast for 2 days. It was administered at 2.5 mg dose twice daily nebulized into the ventilator circuit as per a standardized protocol by a respiratory therapist irrespective of the patient's age and weight. Treatment was continued until the atelectasis had improved. All patients were sedated as per the clinical indication and patients need, and ventilated using pressure-regulated volume control mode. Airway suctioning and chest physiotherapy (CPT) was performed for these patients were administered according to a standardized CICU protocol. The institution of supportive therapies such as chest physiotherapy and suctioning were based on chest x-ray changes and were independent of microscopic findings (PMN and bacteria) in the bronchoalveolar lavage.

Radiology

For the purpose of this study new onset of atelectasis in a patient was defined as the presence of a transient pulmonary parenchymal opacity, which was associated with loss of lung volume when it involved a large portion of a lobe.³⁵ As it is difficult to differentiate atelectasis from pneumonia and focal edema or hemorrhage, the opacity was deemed to represent atelectasis when there was no air bronchogram within the opacity, there were no general signs of vascular fluid overload, and the opacity was absent within 48 hours on subsequent chest radiographs. Antero-posterior chest x-rays before and within 24 hours after treatment with rhDNase were coded, blinded, and interpreted randomly by an independent pediatric radiologist (BG) and an experienced intensivist (UD). Correlation was tested for the chest x-rays between the interpretations of the two investigators. Agreement between the chest x-ray scores by the two observers expressed as Cohen's kappa was 0.92. Each chest x-ray was scored for the degree of atelectasis for each lobe. Atelectasis in mechanically ventilated patient's was classified based on *a priori* defined criteria's where linear atelectasis was scored as 1 point, sub-segmental atelectasis was scored as 2 points and lobar atelectasis was marked as 3 points. The score results were summed for each chest x-ray. The chest x-ray score before rhDNase treatment was compared with the chest x-ray score within 24 hours after treatment.

Statistics

The Fisher exact tests (two tailed) were used to compare frequency distributions obtained from the 2 groups. Ratings obtained from the 2 pediatric radiologists were analyzed using *t* tests and correlation coefficients. The Kruskal-Wallis test was used to compare the effect of rhDNase between baseline and number of doses followed by Dunn's multiple comparison test. A *p* value of <0.05 was considered to be significant.

RESULTS

Baseline Data

Thirty eight patients fulfilled our inclusion criteria's. The median age of the study cohort was 3.5 months (range <1 month to 325 months) (Table 1). 32/ 38 (84%) patients were 5-years-of-age and below. The underlying cardiac diagnosis for the study cohort included those with both cyanotic and acyanotic heart disease (hypoplastic left heart syndrome-9; atrio-ventricular canal defect-6; Tetralogy of Fallot-5; double outlet right ventricle-3; heart transplantation-3; d-transposition of great arteries-3; ventricular septal defect and coarctation of aorta-3; tricuspid atresia-2; truncus arteriosus-1; aortic stenosis-1; vascular sling-1; and paroxysmal junctional re-entrant tachycardia-1). The patient with paroxysmal junctional re-entrant tachycardia required cryoablation and failed extubation secondary to atelectasis and was treated with rhDNase. This patient did not undergo cardiac surgery on cardiopulmonary bypass.

The average length of cardiac ICU stay was 28.9 days (range, 4 days–131 days). 22/ 38 (58%) patients had bacteria present, 32/38 (84%) had PMN present with 24/38 having more than $\geq$ moderate amounts of PMN present, and 29/38 (%) had either bacteria and/ or $\geq$ moderate amounts of PMN present in their pre-rhDNase therapy tracheal aspirate.

Gas exchange and ventilatory parameters

The gas exchange and ventilatory parameters prior to administering rhDNase dose was compared to those after the rhDNase dose was administered. The analysis carried out for the first 5 doses is shown in Table 2. Significant differences in inspired oxygen concentration (FiO₂) were found (p value= <0.001) before and after the rhDNase doses were administered. Even though this change in FiO₂ statistically significant; in real clinical practice this effect is small. However, no significant differences in mean PIP, PEEP, arterial P_aO₂, and P_aCO₂ were found.

Atelectasis Scores

Figure 1. demonstrates a significant difference from baseline chest x-ray atelectasis scores in all the lung fields seen when either < 5 rhDNase doses (p value= < 0.05), 5–10 rhDNase doses (p value= < 0.01) or 10–15 rhDNase doses (p value= < 0.05) were administered. This was also significant for chest x-ray atelectasis scores for the left lower lobe when compared to the baseline when 5–10 rhDNase doses were administered. Data relating to other lung lobes did not show any significant change from baseline.

We found (Figures 2,3,4) that rhDNase was more effective in improving chest x-ray atelectasis score in patients who had $\geq$ moderate amounts of PMN (p value 0.0008), or bacteria (p value=0.007) or either $\geq$ moderate PMN and/ or bacteria (p value =0.004) present in their pre-therapy trachea aspirate.

In the figures rank means refers to the ranking of the degree of the rhDNase therapy effects. Since the values were not numeric, the effects were ranked as 0 for the least effects, 1 for medium effect, and 3 for maximum effect. The overall p -values in the figures show the results of the ANOVA test indicating the level of statistical significance for differences which exist between the multiple groups. Further, the statistical differences between the groups from baseline values are also depicted.

The frequency of chest physiotherapy (CPT) for the comparison groups ($\leq$ few PMN group vs. those with $\geq$ moderate PMN group, and presence of any bacteria vs. none; both $\leq$ few PMN and no bacteria group vs. $\geq$ moderate PMN and bacteria present group) was not

statistically different pre-rhDNase therapy ($p = 0.461, 0.472$ and 0.556 respectively) or after rhDNase therapy was started ($p = 0.878, 0.860$ and 0.955 respectively).

We found no major complications such as immediate desaturations, pulmonary hemorrhage, wheezing or worsening of pulmonary parameters associated with rhDNase therapy in this study.

DISCUSSION

Short term rhDNase is a safe and effective modality for treating established lung atelectasis in children with cardiac disease. Previously, Riethmueller et al¹⁵ have shown that rhDNase therapy was effective in preventing atelectasis and lowered ventilation time, length of ICU stay in rhDNase-treated infants with cardiac disease. However, Riethmueller et al¹⁵, in contrast to our study, used rhDNase in a prophylactic role with the treatment beginning immediately after cardiac surgery irrespective of the presence of prior atelectasis. Further, unlike our study where rhDNase was nebulized, the investigators administered rhDNase by instilling it directly into the indwelling endotracheal tube.

rhDNase also appears to be more effective in improving atelectasis when either bacteria or PMN are present in the pre-therapy tracheal aspirates. Our results are supported by the proposed mechanistic actions of rhDNase which hydrolyzes the DNA rich sputum, transforming it from a viscous gel to a flowing liquid which can be easily removed. Bacterial presence in the sputum leads to the release of pro-inflammatory cytokines and which in turn activates the mucin gene causing excessive mucus production.²³ DNA is released in the airway surface by degenerating inflammatory PMN which along with excess mucus production contributes to airway plugging and atelectasis. These effects are similar to that seen in children with CF¹³ where rhDNase has been extensively used to treat excessive amounts of thick DNA rich airway secretions. However, unlike patients with CF where rhDNase is used predominantly in patients above 5 years of age, the therapeutic effect in our study was seen in much younger children (median age- 3.5 months). Further, atelectasis improved without any significant difference in the frequency of chest physiotherapy among the compared groups.

Our study also indicates that rhDNase is most effective in improving atelectasis within 10 doses of therapy. Thereafter, no significant improvement in atelectasis with increasing number of doses was noted. Previously, a few small studies have shown that short-term rhDNase therapy, ranging from a single dose to less than 3-days improved atelectasis.^{16–20,25–27} However, none of these studies were in mechanically ventilated children with cardiac disease. It is plausible, that the limited clinical response in ameliorating atelectasis beyond 10 doses may be because respiratory secretions get inspissated once in place for prolonged duration of time and become less responsive to the mucolytic properties of rhDNase. Our results do not support the continuation of rhDNase therapy if no improvement in atelectasis is observed by 10 to 15 doses.

The nebulized therapy appeared safe and was easily administered. There were no adverse effects identified in the study cohort which included many patients were newborns and children below the age of 5-years where the experience with this therapy is limited.

There are several limitations to this study. As a retrospective study it may suffer from selection bias even though we took consecutive patients during the study period. The study cohort due to its small sample size, multiple cardiac diagnoses, and varying clinical course precludes us from evaluating the role of the therapy on outcomes such as hospital/ ICU length of stay. Even though we found no significant differences between the frequency of chest physiotherapy the groups the contribution of the concurrently administered aggressive

chest physiotherapy regimen to these patients cannot be fully deduced from this study. We did not find a validated scoring system for atelectasis on chest radiographs in mechanically ventilated children in the literature. However, we used an *a priori* defined classification consistently with good agreement between the experts reading the chest radiographs. Further, atelectasis and infiltrate are difficult to differentiate on chest x-rays and could be incorrectly interpreted. However, we have tried to overcome this limitation by having two independent investigators blinded to the outcomes interpret the chest x-ray findings. This study is not designed to answer whether rhDNase was more effective in those patients with higher sputum DNA content as no analysis of the sputum DNA content was carried out. Other limitations are the lack of changes in respiratory parameters such as compliance and oxygenation index.

CONCLUSIONS

rhDNase is helpful in our group of patients in treating established atelectasis and appears to be safe even when used in infants and children below 5-years-of-age. The therapeutic effect seems to be most effective within 10 doses. This descriptive study highlights rhDNase as a therapeutic option in the treatment of atelectasis in post cardiac surgery requiring mechanically ventilation. However larger randomized studies using rhDNase for established atelectasis are essential to establish the criteria of the use rhDNase.

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Figure 1.

Demonstrates significant difference from baseline chest radiographic atelectasis scores when comparing administration of either < 5 rhDNase doses (p value= < 0.05), 5–10 rhDNase doses (p value= < 0.01) doses or 10–15 rhDNase doses (p value= < 0.05) for all lung fields combined. This was also significant for only left lower lobe atelectasis when comparing the baseline chest radiographic atelectasis scores to the 5–10 rhDNase doses administered.

*: $p < 0.05$

** : $p < 0.01$

Figure 2.

Demonstrates that rhDNase was more effective in those patients who had > few polymorphonuclear neutrophils present in their pre-therapy trachea aspirate (p value= 0.0008).

*: $p<0.05$

** : $p<0.01$

Figure 3.

Shows that rhDNase is more effective in those patients with the presence of bacteria in their pre-therapy tracheal aspirate (p value= 0.007).

*: p<0.05

Figure 4.

Shows that rhDNase is more effective in those patients with the presence of bacteria and/ or > few polymorphonuclear neutrophils in their pre-therapy tracheal aspirate (p value= 0.0041)

*: p<0.05

Table 1

Demographics

Variable	N
Age (months): Median (range)	3.5 (<1–325)
Male Gender	23
Race: White/African American/Hispanic	24/12/2
Average Days in ICU; median (range)	28.9 (4–31)
Bacteria: Absent /present	16/22
Neutrophils: Absent/ present	6/32
Cardiac Lesion (Cyanotic/ Acyanotic)	22/16

Table 2

Comparison of Physiologic and Ventilator Variables before and after rhDNaseTherapy

Variables Studied (mean)	First 5 Doses Pre- rhDNase	First 5 Doses Post rhDNase	<i>P</i> Value ^I
PIP (cm H ₂ O)	19.58	19.20	0.80
PEEP (cm H ₂ O)	7.6	6.92	0.65
FiO ₂	0.45	0.40	<0.0001
PaO ₂ (mm Hg)	73.41	76.47	0.72
PaCO ₂ (mm Hg)	46.8	48.2	0.65

PIP=Peak inspiratory pressure; PEEP=Peak end expiratory pressure; FiO₂= inspired oxygen concentration; PaCO₂= arterial CO₂ pressure; PaO₂= arterial O₂ pressure

^I *P* value < 0.05 significant;