Stratified Assessment of the Role of Inhaled Hypertonic Saline in Reducing Cystic Fibrosis Pulmonary Exacerbations

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Abstract:	Objective: Limited data exist concerning the role of inhaled hypertonic saline (HS) in decreasing pulmonary exacerbations in cystic fibrosis (CF), especially as more advanced stages of CF lung disease were excluded in prior studies. Herein we retrospectively determined the efficacy of inhaled HS in decreasing the frequency of pulmonary exacerbations in patients stratified according to the severity of CF lung disease. Stratification was based on the framework of the Pulmonary Therapeutics Committee's published gradation of obstructive lung physiology in CF, i.e., mild (FEV1 > 70%), moderate (FEV1 40-70%) and severe (FEV1 < 40%) lung disease, respectively. Design: A retrospective review of the Port CF® database over a 3-year period performed at an academic CF care center. Results: 340 pulmonary exacerbations were identified; inhaled HS was being used in 99 of these cases. Exacerbations were significantly reduced among patients using HS with mild obstructive CF lung disease (OR=0.09, CI 0.01-0.81, p=0.01), whereas there was no significant reduction among patients with moderate (OR=1.33, CI 0.65-2.74, p=0.432) and severe CF lung disease (OR=5.62, CI 0.73-43.21, p=0.063). Moreover, inhaled HS appeared reasonably well tolerated across all stages of lung disease severity, and was discontinued in only 7% of cases (n=4) with severe lung disease. Conclusion: In this study, inhaled HS significantly reduced pulmonary exacerbations in CF lung disease of mild severity, but not in more advanced stages. This underscores the importance of initiating inhaled HS early on in the CF disease process.

Title Page

Title: Stratified Assessment of the Role of Inhaled Hypertonic Saline in Reducing Cystic Fibrosis Pulmonary Exacerbations

Running Head: Inhaled hypertonic saline in CF lung disease

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Abstract

Objective: Limited data exist concerning the role of inhaled hypertonic saline (HS) in decreasing pulmonary exacerbations in cystic fibrosis (CF), especially as more advanced stages of CF lung disease were excluded in prior studies. Herein we retrospectively determined the efficacy of inhaled HS in decreasing the frequency of pulmonary exacerbations in patients stratified according to the severity of CF lung disease. Stratification was based on the framework of the Pulmonary Therapeutics Committee's published gradation of obstructive lung physiology in CF, i.e., mild ($FEV_1 > 70\%$), moderate (FEV_1 40-70%) and severe ($FEV_1 < 40\%$) lung disease, respectively.

Design: A retrospective review of the Port CF® database over a 3-year period performed at an academic CF care center.

Results: 340 pulmonary exacerbations were identified; inhaled HS was being used in 99 of these cases. Exacerbations were significantly reduced among patients using HS with mild obstructive CF lung disease (OR=0.09, CI 0.01-0.81, p=0.01), whereas there was no significant reduction among patients with moderate (OR=1.33, CI 0.65-2.74, p=0.432) and severe CF lung disease (OR=5.62, CI 0.73-43.21, p=0.063). Moreover, inhaled HS appeared reasonably well tolerated across all stages of lung disease severity, and was discontinued in only 7% of cases (n=4) with severe lung disease.

Conclusion: In this study, inhaled HS significantly reduced pulmonary exacerbations in CF lung disease of mild severity, but not in more advanced stages. This underscores the importance of initiating inhaled HS early on in the CF disease process.

Article Summary

Article focus:

- Inhaled hypertonic saline (HS) improved the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) in patients with cystic fibrosis.
- Inhaled HS also decreases the frequency of pulmonary exacerbations in cystic fibrosis; this aspect has been less extensively studied, especially in more severe forms of disease.
- This study focuses on establishing the role of inhaled HS in decreasing the frequency of pulmonary exacerbations in patients stratified according to the severity of CF lung disease.

Key messages:

- This study confirms the benefits of inhaled HS in reducing exacerbations in patients with mild CF lung disease; a similar effect was not observed in subjects with moderate and severe forms of CF lung disease, ostensibly from greater degrees of irreversible airway pathology.
- The observed benefit of inhaled HS appeared in addition to that of established airway clearance strategies such as nebulized rhDNase therapy and mechanical airway clearance devices.
- This study found no indication of any excessive discontinuation of inhaled HS due to cough or bronchospasm in more severe forms of CF lung disease, suggesting that it is reasonably well tolerated even in such cases.

Strengths and limitations of this study:

- This study assessed the effects of inhaled HS in reducing the number of pulmonary exacerbations across varying levels of lung disease severity, especially considering that more severe forms of CF lung disease had been previously excluded.

- Our study group had a significantly higher usage of nebulized rhDNase (100%) and other mechanical airway clearance therapies (97%) compared to previous studies, thus supporting the additional beneficial effect of inhaled HS.

- The two study groups had differences in epidemiological characteristics, lending bias to our interpretation. Furthermore, a regression analysis to adjust for clinical and epidemiological characteristics was not performed.

Introduction

Cystic fibrosis (CF) is characterized by decreased clearance of airway mucus that over time leads to progressive inflammatory loss of lung function consequent to infectious exacerbations.[1] In this context, the landmark trial of Elkins and colleagues [2] established that inhaled hypertonic 7% saline (HS) nebulized twice daily in CF lung disease improved the overall forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) by 68 ml and 82 ml, respectively, although it did not appreciably alter the rate of decline of FEV_1. The effect of inhaled HS in decreasing the frequency of clinical exacerbations of CF lung disease was reported as a secondary outcome in this trial.[2] Prior to this report, other trials had likewise demonstrated the short-term benefit of HS,[3, 4] but had not specifically addressed the effect of inhaled HS in decreasing pulmonary exacerbations in CF lung disease. We sought to better define the therapeutic role of inhaled HS in reducing the frequency of pulmonary exacerbations based on the severity of underlying CF lung disease; this is in accordance with the current stratified framework of evidence-based Cystic Fibrosis Pulmonary Guidelines.[5] The original abstract of this study was presented at the 2009 annual scientific meeting of the American College of Chest Physicians.[6]

Methods

A retrospective assessment of the Port CF® database was performed at an accredited CF care academic center. Approval was obtained from the Institutional Review Board at Saint Louis University. We initially identified a cohort of CF patients who presented over a three-year period beginning January 2006, corresponding to the publication of the Elkins study.[2] All episodes of pulmonary exacerbations necessitating either hospitalization or treatment with home intravenous antibiotics were identified. Other recorded variables included utilization of inhaled HS, airway

clearance methodologies, demographics, sputum culture results, and spirometric indices. Comparison between groups was performed utilizing Chi-Square and independent *t*-testing for categorical and continuous variables, respectively. Severity of CF lung disease was further stratified into three groups based on the framework of the Pulmonary Therapeutics Committee's published gradation of obstructive lung physiology in CF,[5] i.e., mild (FEV_1 > 70% predicted), moderate (FEV_1 40-70% predicted) and severe (FEV_1 < 40% predicted) lung disease, respectively. Univariate Chi-Square analysis was performed separately in all three subgroups to assess the effects of HS in reducing the frequency of pulmonary exacerbations; consequently, a p-value of 0.016 was considered significant utilizing a Bonferroni adjustment for multiple comparisons. Statistical analysis was performed using SPSS version 17 (SPSS Inc., Chicago, IL)

Results

Overall, 340 pulmonary exacerbations were identified. The average age of the entire cohort was 31 $\pm$ 11 years and 55% were male. Inhaled HS was being used in 99/340 cases with exacerbations (29%). 50 patients (12%), 183 patients (45%) and 170 patients (42%) of the cohort were categorized as having mild, moderate and severe CF lung disease, respectively; 21 patients were uncategorized secondary to unclear documentation of the FEV_1. Demographic and clinical variables are summarized in Table 1. We found a significant reduction in pulmonary exacerbations in the subgroup of patients using HS with mild lung disease (OR=0.09, CI 0.01-0.81, *p*=0.012), whereas no reductions were found in the cohort of subjects with moderate (OR=1.33, CI 0.65-2.74, *p*=0.432) and severe lung disease (OR=5.62, CI 0.73-43.21, *p*=0.063). These findings are summarized in Table 2. Additionally, inhaled HS was discontinued in only 4 cases (7%) with severe lung disease.

Table 1. Baseline epidemiological characteristics between Hypertonic saline treated and non-treated groups

		Hypertonic Saline (n=121)	**No hypertonic Saline (n=303)**	***p*-value**
Age	*Mean ± SD*	33 ± 10	31 ± 12	0.13
Male Gender	*n (%)*	37 (31%)	196 (65%)	<0.001
Body Mass Index	*Mean ± SD*	20.8 ± 0.7	21.9 ± 5.7	0.001
FEV1 (% predicted)	*Mean ± SD*	50 ± 12	46 ± 23	0.016
FVC (% predicted)	*Mean ± SD*	73 ± 9	57 ± 24	<0.001
Use of rhDNase	*n (%)*	121 (100%)	303 (100%)	n/a
Sputum Positivity for Pseudomonas aeruginosa	*n (%)*	60 (50%)	211 (70%)	<0.001
Sputum Positivity for MRSA	*n (%)*	60 (50%)	97 (32%)	0.001

FEV1 = Forced Expiratory Volume in one second

FVC = Forced Vital Capacity

rhDNase = Recombinant human DNase

MRSA = Methicillin-resistant Staphylococcus Aureus

Table 2. Odds ratios between varying stages of lung disease severity when comparing frequency of pulmonary exacerbation to use of inhaled hypertonic saline

Lung Disease Severity	Odds Ratio	Confidence Intervals		*p*-value
		Lower	Higher	
Mild (*n*=50)	0.09	0.01	0.812	0.012
Moderate (*n*=183)	1.33	0.65	2.74	0.432
Severe (*n*=170)	5.62	0.73	43.21	0.063

Discussion

Exacerbations of CF lung disease account for appreciable morbidity and burden of this disease, which collectively greatly decrease physical functioning and psychosocial quality of life.[7] Pulmonary exacerbations in particular significantly contribute to the overall cost of CF care, accounting for up to 47% of overall costs in one study.[8] Accordingly, measures to decrease pulmonary exacerbations are important. Inhaled HS decreases the viscosity of pulmonary secretions and thereby improves the rheologic properties of mucus secondary to hydration of the airway surface.[9] In addition, HS osmotically induces a sustained increase in the airway surface liquid volume depth, possibly allowing the cilia to beat freely by re-coupling the mucociliary mechanism.[10] Inhaled HS for CF lung disease is currently assigned a Grade II recommendation in the Cystic Fibrosis Pulmonary Guidelines published in 2007,[5] based on evidence from the above-cited trials.[2-4] Notably, in the trial reporting the efficacy of HS in reducing clinical exacerbations,[2] patients with severe CF lung disease (as classified by FEV_1 <

40% predicted) were excluded; moreover, only approximately one-third of the included participants were using nebulized rhDNase.

Here, we have assessed the effects of inhaled HS in reducing the number of pulmonary exacerbations across varying levels of lung disease severity, especially considering that more severe forms of CF lung disease had been previously excluded.[2] Our study confirms the benefits of inhaled HS in reducing exacerbations in patients with mild CF lung disease, which underscores the potential therapeutic benefit of initiating inhaled HS early in the disease process. We could determine no effect of inhaled HS in subjects with moderate and severe forms of CF lung disease, ostensibly from greater degrees of irreversible airway pathology. Our study group had a significantly higher usage of nebulized rhDNase (100%) and other mechanical airway clearance therapies (97%) compared to previous studies.[2] Hence, we postulate that there is an additional benefit of inhaled HS in patients who are already on established airway clearance strategies. We also found no indication of any excessive discontinuation of inhaled HS due to cough or bronchospasm in more severe forms of CF lung disease, suggesting that it is reasonably well tolerated even in such cases.

Even so, the methodological limitations of our study must be acknowledged, principally its retrospective nature and lack of randomization. There was no uniform protocol in place to assess compliance with therapy. Furthermore, the two study groups had differences in epidemiological characteristics, lending bias to our interpretation. In this context, regression analysis to adjust for these variable clinical and epidemiological characteristics was likewise not performed. Ultimately, prospective randomized controlled studies with larger numbers of included participants are warranted to better assess the apparent lack of benefit in patients with moderate and severe CF lung disease.

Conclusion

Our study demonstrated that pulmonary exacerbations are significantly reduced in patients with CF lung disease of mild severity during active use of inhaled HS. The beneficial effect of HS was additive to other airway clearance measures such as nebulized rhDNase and mechanical clearance strategies. Moreover, inhaled HS appeared reasonably well tolerated. Recently, the effectiveness of alternative therapies such as nebulized mannitol for mucociliary clearance has been reported.[11] Until these newer strategies are better established, we support the use of inhaled HS in CF lung disease, in the context of reducing pulmonary exacerbations. This is especially so given the potential to improve lung function, quality of life, CF-related costs, and possibly mortality.[1, 7, 8, 12, 13]

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Stratified Assessment of the Role of Inhaled Hypertonic Saline in Reducing Cystic Fibrosis Pulmonary Exacerbations: A Retrospective Analysis

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Title Page

Title: Stratified Assessment of the Role of Inhaled Hypertonic Saline in Reducing Cystic Fibrosis Pulmonary Exacerbations: A Retrospective Analysis

Running Head: Inhaled hypertonic saline in CF lung disease

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Abstract

Objective: Limited data exist concerning the role of inhaled hypertonic saline (HS) in decreasing pulmonary exacerbations in cystic fibrosis (CF), especially as more advanced stages of CF lung disease were excluded in prior studies. Herein we retrospectively determined the efficacy of inhaled HS in reducing CF pulmonary exacerbations when stratified according to the severity of CF lung disease. Stratification was based on the framework of the Pulmonary Therapeutics Committee's published gradation of obstructive lung physiology in CF, i.e., mild (FEV_1 > 70%), moderate (FEV_1 40-70%) and severe (FEV_1 < 40%) lung disease, respectively.

Design: A retrospective review of the Port CF® database over a 3-year period performed at an academic CF care center.

Results: 340 pulmonary exacerbations were identified; inhaled HS was being used in 99 of these cases. Univariate analysis demonstrated a significant reduction in pulmonary exacerbations only in mild obstruction (OR=0.09, CI 0.01-0.81, *p*=0.012); however, multivariate logistic regression showed a reduction in pulmonary exacerbations across the entire spectrum of obstructive lung disease when using inhaled HS i.e., mild obstructive CF lung disease (OR=0.17, CI 0.05-0.58, *p*=0.004), moderate obstructive CF lung disease (OR=0.39, CI 0.16-0.93, *p*=0.034), as well as severe obstructive CF lung disease (OR=0.02, CI 0.001-0.45, *p*=0.015). Moreover, inhaled HS appeared reasonably well tolerated across all stages of lung disease severity, and was discontinued in only 7% of cases (*n*=4) with severe lung disease.

Conclusion: In this study, inhaled HS significantly reduced pulmonary exacerbations in CF lung disease at all stages of obstruction. This underscores the importance of therapeutic inhaled HS in CF lung disease, regardless of severity of lung obstruction.

Article Summary

Article focus:

- Inhaled hypertonic saline (HS) improves the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) in patients with cystic fibrosis.
- Inhaled HS also decreases the frequency of pulmonary exacerbations in cystic fibrosis; this aspect has been less extensively studied, especially in more severe forms of disease.
- This study focuses on the role of inhaled HS in decreasing the frequency of pulmonary exacerbations in patients stratified according to the severity of CF lung disease.

Key messages:

- This study confirms the benefits of inhaled HS in reducing pulmonary exacerbations at all stages of CF lung disease severity, thus highlighting the importance of inhaled HS as a key component of the CF therapeutic armamentarium.
- The observed benefit of inhaled HS appeared in addition to that of established airway clearance strategies such as nebulized rhDNase therapy and mechanical airway clearance devices.
- This study found no indication of any excessive discontinuation of inhaled HS due to cough or bronchospasm in more severe forms of CF lung disease, suggesting that it is reasonably well tolerated even in such cases.

Strengths and limitations of this study:

- This study establishes the role of inhaled HS in reducing the number of pulmonary exacerbations at more advanced stages of CF lung disease severity, which is of special significance considering that the more severe forms of CF lung disease had been excluded in previous studies.

- Our study group had a significantly higher usage of nebulized rhDNase (100%) and other mechanical airway clearance therapies (97%) compared to previous studies, thus supporting the additional beneficial effect of inhaled HS.

- Our two study groups had differences in epidemiological characteristics, potentially introducing bias into the results. We have attempted to minimize for this by performing a logistic regression; however, we acknowledge the inherent limitations of such a retrospective study design.

Introduction

Cystic fibrosis (CF) is characterized by decreased clearance of airway mucus that over time leads to progressive inflammatory loss of lung function consequent to infectious exacerbations.[1] In this context, the landmark trial of Elkins and colleagues [2] established that inhaled hypertonic 7% saline (HS) nebulized twice daily in CF lung disease improved the overall forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) by 68 ml and 82 ml, respectively, although it did not appreciably alter the rate of decline of FEV_1. The effect of inhaled HS in decreasing the frequency of clinical exacerbations of CF lung disease was reported as a secondary outcome in this trial.[2] Prior to this report, other trials had likewise demonstrated the short-term benefit of HS,[3, 4] but had not specifically addressed the effect of inhaled HS in decreasing pulmonary exacerbations in CF lung disease. We sought to better define the therapeutic role of inhaled HS in reducing the frequency of pulmonary exacerbations based on the severity of underlying CF lung disease; this is in accordance with the current stratified framework of evidence-based Cystic Fibrosis Pulmonary Guidelines.[5] The original abstract of this study was presented at the 2009 annual scientific meeting of the American College of Chest Physicians.[6]

Methods

A retrospective assessment of the Port CF® database was performed at an accredited CF care academic center. Approval was obtained from the Institutional Review Board at Saint Louis University. We initially identified a cohort of CF patients who presented over a three-year period beginning January 2006, corresponding to the publication of the Elkins study.[2] All episodes of pulmonary exacerbations necessitating either hospitalization or treatment with home intravenous antibiotics were identified. Other recorded variables included utilization of inhaled HS, airway

clearance methodologies, demographics, sputum culture results, and spirometric indices. Comparison between groups was performed utilizing Chi-Square and independent *t*-testing for categorical and continuous variables, respectively. Severity of CF lung disease was further stratified into three groups based on the framework of the Pulmonary Therapeutics Committee's published gradation of obstructive lung physiology in CF,[5] i.e., mild ($FEV_1 > 70\%$ predicted), moderate (FEV_1 40-70% predicted) and severe ($FEV_1 < 40\%$ predicted) lung disease, respectively. Univariate Chi-Square analysis was performed separately in all three subgroups to assess the effects of HS in reducing the frequency of pulmonary exacerbations; consequently, a p-value of 0.016 was considered significant utilizing a Bonferroni adjustment for multiple comparisons. Finally, logistic regression was also performed in all subgroups to adjust for differences in subgroup characteristics such as age, gender, BMI, inhaled HS, sputum positivity for MRSA or Pseudomonas, as well as the spirometric FEV_1 and FVC. Statistical analysis was performed using SPSS version 17 (SPSS Inc., Chicago, IL).

Results

Overall, 340 pulmonary exacerbations were identified. The average age of the entire cohort was 31 $\pm$ 11 years and 55% were male. Inhaled HS was being used in 99/340 cases with exacerbations (29%). 50 patients (12%), 183 patients (45%) and 170 patients (42%) of the cohort were categorized as having mild, moderate and severe CF lung disease, respectively; 21 patients were uncategorized secondary to unclear documentation of the FEV_1. Demographic and clinical variables are summarized in Table 1. Using univariate analysis, we found a significant reduction in pulmonary exacerbations in the subgroup of patients using HS with mild lung disease (OR=0.09, CI 0.01-0.81, p=0.012), whereas no reductions were found in the cohort of subjects with moderate (OR=1.33, CI 0.65-2.74, p=0.432) and severe lung disease (OR=5.62, CI 0.73-

43.21, *p*=0.063). However, subsequent multivariate analysis using logistic regression modeling demonstrated a reduction in pulmonary exacerbations when using HS at all stages of obstruction i.e., mild obstructive CF lung disease (OR=0.17, CI 0.05-0.58, *p*=0.004), moderate obstructive CF lung disease (OR=0.39, CI 0.16-0.93, *p*=0.034), as well as severe obstructive CF lung disease (OR=0.02, CI 0.001-0.45, *p*=0.015). These findings are summarized in Tables 2 and 3, with individual regression tables in the supplementary appendix. Additionally, inhaled HS was discontinued in only 4 cases (7%) with severe lung disease.

Table 1. Baseline epidemiological characteristics between hypertonic saline treated and non-treated groups

		Hypertonic Saline (n=121)	No hypertonic Saline (n=303)	*p*-value
Age	*Mean ± SD*	33 ± 10	31 ± 12	0.13
Male Gender	*n (%)*	37 (31%)	196 (65%)	<0.001
Body Mass Index	*Mean ± SD*	20.8 ± 0.7	21.9 ± 5.7	0.001
FEV1 (% predicted)	*Mean ± SD*	50 ± 12	46 ± 23	0.016
FVC (% predicted)	*Mean ± SD*	73 ± 9	57 ± 24	<0.001
Use of rhDNase	*n (%)*	121 (100%)	303 (100%)	n/a
Sputum Positivity for Pseudomonas aeruginosa	*n (%)*	60 (50%)	211 (70%)	<0.001
Sputum Positivity for MRSA	*n (%)*	60 (50%)	97 (32%)	0.001
Airway clearance device (Chest Vest OR flutter valve)	*n (%)*	80 (93%)	143 (97%)	
Hospitalization / Home i.v. antibiotics	*n (%)*	41 (52%) / 41 (48%)	88 (60%) / 60(40%)	

FEV1 = Forced Expiratory Volume in one second

FVC = Forced Vital Capacity

rhDNase = Recombinant human DNase

MRSA = Methicillin-resistant Staphylococcus Aureus

Table 2. Odds ratios using inhaled hypertonic saline for pulmonary exacerbations using univariate analysis

Lung Disease Severity	Odds Ratio	Confidence Intervals		*p*-value
		Lower	Higher	
Mild (*n*=50)	0.09	0.01	0.812	**0.012**
Moderate (*n*=183)	1.33	0.65	2.74	0.432
Severe (*n*=170)	5.62	0.73	43.21	0.063

Table 2. Odds ratios using inhaled hypertonic saline for pulmonary exacerbations using multivariate analysis

Lung Disease Severity	Odds Ratio	Confidence Intervals		*p*-value
		Lower	Higher	
Mild (*n*=50)	0.17	0.05	0.58	**0.004**
Moderate (*n*=183)	0.39	0.16	0.93	**0.034**
Severe (*n*=170)	0.02	0.001	0.452	**0.015**

Discussion

Exacerbations of CF lung disease account for appreciable morbidity and burden of this disease, which collectively greatly decrease physical functioning and psychosocial quality of life.[7] Pulmonary exacerbations in particular significantly contribute to the overall cost of CF care, accounting for up to 47% of overall costs in one study.[8] Accordingly, measures to decrease

pulmonary exacerbations are important. Inhaled HS decreases the viscosity of pulmonary secretions and thereby improves the rheologic properties of mucus secondary to hydration of the airway surface.[9] In addition, HS osmotically induces a sustained increase in the airway surface liquid volume depth, possibly allowing the cilia to beat freely by re-coupling the mucociliary mechanism.[10] Inhaled HS for CF lung disease is currently assigned a Grade II recommendation in the Cystic Fibrosis Pulmonary Guidelines published in 2007,[5] based on evidence from the above-cited trials.[2-4] Notably, in the trial reporting the efficacy of HS in reducing clinical exacerbations,[2] patients with severe CF lung disease (as classified by FEV_1 < 40% predicted) were excluded; moreover, only approximately one-third of the included participants were using nebulized rhDNase.

Here, we have assessed the effects of inhaled HS in reducing the number of pulmonary exacerbations across varying levels of lung disease severity, especially considering that more severe forms of CF lung disease had been previously excluded.[2] Our study confirms the benefits of inhaled HS in reducing exacerbations across all stages of CF lung disease using multivariate analyses, even though univariate analysis only showed benefit in mild CF lung disease. These findings underscore the potential therapeutic benefit of initiating inhaled HS at any stage in the disease continuum. Our study group had a significantly higher usage of nebulized rhDNase (100%) and other mechanical airway clearance therapies (97%) compared to previous studies.[2] Hence, we postulate that there is an additional benefit of inhaled HS in patients who are already on established airway clearance strategies. We also found no indication of any excessive discontinuation of inhaled HS due to cough or bronchospasm in more severe forms of CF lung disease, suggesting that it is reasonably well tolerated even in such cases.

Even so, the methodological limitations of our study must be acknowledged, principally its retrospective nature and lack of randomization. There was no uniform protocol in place to assess compliance with therapy. Furthermore, the two study groups had differences in epidemiological characteristics, lending bias to our interpretation; although, in this context, regression analysis in an attempt to adjust for these variable clinical and epidemiological characteristics was performed. However, ultimately, prospective randomized controlled studies with larger numbers of included participants are warranted to better assess the benefit of inhaled HS at varying stages of CF lung disease severity.

Conclusion

Our study demonstrated that pulmonary exacerbations are significantly reduced in patients with CF lung disease of any severity during active use of inhaled HS. The beneficial effect of HS was additive to other airway clearance measures such as nebulized rhDNase and mechanical clearance strategies. Moreover, inhaled HS appeared reasonably well tolerated. Recently, the effectiveness of alternative therapies such as nebulized mannitol for mucociliary clearance has been reported.[11] Until these newer strategies are better established, we support the use of inhaled HS in CF lung disease, in the context of reducing pulmonary exacerbations. This is especially so given the potential to improve lung function, quality of life, CF-related costs, and possibly mortality.[1, 7, 8, 12, 13]

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Contributorship Statement

Dr. Dmello was involved in conception and design of the study, data analysis as well as authoring and revising the manuscript. Dr. Nayak and Dr. Matuschak were involved in the design of the study as well as in manuscript revision. All authors have reviewed and approved the final version of the manuscript.

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Stratified Assessment of the Role of Inhaled Hypertonic Saline in Reducing Cystic Fibrosis Pulmonary Exacerbations: A Retrospective Analysis

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Title Page

Title: Stratified Assessment of the Role of Inhaled Hypertonic Saline in Reducing Cystic Fibrosis Pulmonary Exacerbations: A Retrospective Analysis

Running Head: Inhaled hypertonic saline in CF lung disease

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Abstract

Objective: Limited data exist concerning the role of inhaled hypertonic saline (HS) in decreasing pulmonary exacerbations in cystic fibrosis (CF), especially as more advanced stages of CF lung disease were excluded in prior studies. Herein we retrospectively determined the efficacy of inhaled HS in reducing CF pulmonary exacerbations when stratified according to the severity of CF lung disease. Stratification was based on the framework of the Pulmonary Therapeutics Committee's published gradation of obstructive lung physiology in CF, i.e., mild (FEV_1 > 70%), moderate (FEV_1 40-70%) and severe (FEV_1 < 40%) lung disease, respectively.

Design: A retrospective review of the Port CF® database over a 3-year period performed at an academic CF care center.

Results: 340 pulmonary exacerbations were identified; inhaled HS was being used in 99 of these cases. Univariate analysis demonstrated a significant reduction in pulmonary exacerbations only in mild obstruction (OR=0.09, CI 0.01-0.81, *p*=0.012); however, multivariate logistic regression that adjusted for confounding variables showed a reduction in pulmonary exacerbations across the entire spectrum of obstructive lung disease when using inhaled HS i.e., mild obstructive CF lung disease (OR=0.17, CI 0.05-0.58, *p*=0.004), moderate obstructive CF lung disease (OR=0.39, CI 0.16-0.93, *p*=0.034), as well as severe obstructive CF lung disease (OR=0.02, CI 0.001-0.45, *p*=0.015). Moreover, inhaled HS appeared reasonably well tolerated across all stages of lung disease severity, and was discontinued in only 7% of cases (*n*=4) with severe lung disease.

Conclusion: In this study, inhaled HS appeared to reduce pulmonary exacerbations in CF lung disease at all stages of obstruction. This underscores the importance of therapeutic inhaled HS in CF lung disease, regardless of severity of lung obstruction.

Article Summary

Article focus:

- Prior studies have demonstrated that inhaled hypertonic saline (HS) improves the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) in patients with cystic fibrosis.
- Inhaled HS also decreases the frequency of pulmonary exacerbations in cystic fibrosis; this aspect has been less extensively studied, especially in more severe forms of disease.
- This study focuses on the role of inhaled HS in decreasing the frequency of pulmonary exacerbations in patients stratified according to the severity of CF lung disease.

Key messages:

- This study suggests that inhaled HS may be beneficial in reducing pulmonary exacerbations at all stages of CF lung disease severity, thus highlighting the importance of inhaled HS as a key component of the CF therapeutic armamentarium.
- The observed benefit of inhaled HS appeared in addition to that of established airway clearance strategies such as nebulized rhDNase therapy and mechanical airway clearance devices.
- This study found no indication of any excessive discontinuation of inhaled HS due to cough or bronchospasm in more severe forms of CF lung disease, suggesting that it is reasonably well tolerated even in such cases.

Strengths and limitations of this study:

- This study establishes the role of inhaled HS in reducing the number of pulmonary exacerbations at more advanced stages of CF lung disease severity, which is of special significance considering that the more severe forms of CF lung disease had been excluded in previous studies.

- Our study group had a significantly higher usage of nebulized rhDNase (100%) and other mechanical airway clearance therapies (97%) compared to previous studies, thus supporting the additional beneficial effect of inhaled HS.

- Our two study groups had differences in epidemiological characteristics, potentially introducing bias into the results. We have attempted to minimize for this by performing a logistic regression; however, we acknowledge the inherent limitations of such a retrospective study design.

Introduction

Cystic fibrosis (CF) is characterized by decreased clearance of airway mucus that over time leads to progressive inflammatory loss of lung function consequent to infectious exacerbations.[1] In this context, the landmark trial of Elkins and colleagues [2] established that inhaled hypertonic 7% saline (HS) nebulized twice daily in CF lung disease improved the overall forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) by 68 ml and 82 ml, respectively, although it did not appreciably alter the rate of decline of FEV_1. The effect of inhaled HS in decreasing the frequency of clinical exacerbations of CF lung disease was reported as a secondary outcome in this trial; a 56% relative reduction in exacerbations for the HS-treated group [2]. Prior to this report, other trials had likewise demonstrated the short-term benefit of HS,[3, 4] but had not specifically addressed the effect of inhaled HS in decreasing pulmonary exacerbations in CF lung disease. We sought to better define the therapeutic role of inhaled HS in reducing the frequency of pulmonary exacerbations based on the severity of underlying CF lung disease; this is in accordance with the current stratified framework of evidence-based Cystic Fibrosis Pulmonary Guidelines.[5] The original abstract of this study was presented at the 2009 annual scientific meeting of the American College of Chest Physicians.[6]

Methods

A retrospective assessment of the Saint Louis University (SLU) institutional data within the Port CF® database registry was performed. The SLU CF care center is a combined adult and pediatric academic accredited CF center. The Port CF registry captures both clinical and epidemiologic data from all CF patient during each individual visit to the CF care center, and is recorded as per an established nationwide protocol. Approval was obtained from the Institutional Review Board at Saint Louis University. We initially identified a cohort of CF patients who presented over a

three-year period beginning January 2006, corresponding to the publication of the Elkins study.[2] All episodes of pulmonary exacerbations necessitating either hospitalization or treatment with home intravenous antibiotics were identified. Other recorded variables included utilization of inhaled HS, airway clearance methodologies, demographics, sputum culture results, and spirometric indices. Comparison between groups was performed utilizing Chi-Square and independent *t*-testing for categorical and continuous variables, respectively. Severity of CF lung disease was further stratified into three groups based on the framework of the Pulmonary Therapeutics Committee's published gradation of obstructive lung physiology in CF,[5] i.e., mild (FEV_1 > 70% predicted), moderate (FEV_1 40-70% predicted) and severe (FEV_1 < 40% predicted) lung disease, respectively. Univariate Chi-Square analysis was performed separately in all three subgroups to assess the effects of HS in reducing the frequency of pulmonary exacerbations; consequently, a p-value of 0.016 was considered significant utilizing a Bonferroni adjustment for multiple comparisons. Finally, logistic regression was also performed in all subgroups to adjust for differences in subgroup characteristics such as age, gender, BMI, inhaled HS, sputum positivity for MRSA or Pseudomonas, as well as the spirometric FEV_1 and FVC. Statistical analysis was performed using SPSS version 17 (SPSS Inc., Chicago, IL).

Results

Overall, 340 pulmonary exacerbations were identified from a cohort of 424 patients. The average age of the entire cohort was 31 $\pm$ 11 years and 55% were male. Inhaled HS was being used in 99/340 cases with exacerbations (29%). 50 patients (12%), 183 patients (45%) and 170 patients (42%) of the cohort were categorized as having mild, moderate and severe CF lung disease, respectively; 21 patients were uncategorized secondary to unclear documentation of the FEV_1. Demographic and clinical variables are summarized in Table 1. Using univariate analysis, we

found a significant reduction in pulmonary exacerbations in the subgroup of patients using HS with mild lung disease (OR=0.09, CI 0.01-0.81, *p*=0.012), whereas no reductions were found in the cohort of subjects with moderate (OR=1.33, CI 0.65-2.74, *p*=0.432) and severe lung disease (OR=5.62, CI 0.73-43.21, *p*=0.063). However, subsequent multivariate analysis using logistic regression modeling demonstrated a reduction in pulmonary exacerbations when using HS at all stages of obstruction i.e., mild obstructive CF lung disease (OR=0.17, CI 0.05-0.58, *p*=0.004), moderate obstructive CF lung disease (OR=0.39, CI 0.16-0.93, *p*=0.034), as well as severe obstructive CF lung disease (OR=0.02, CI 0.001-0.45, *p*=0.015). These findings are summarized in Tables 2 and 3, with individual regression tables in the supplementary appendix. Additionally, inhaled HS was discontinued in only 4 cases (7%) with severe lung disease.

Table 1. Baseline epidemiological characteristics between hypertonic saline treated and non-treated groups

		Hypertonic Saline (n=121)	No hypertonic Saline (n=303)	*p*-value
Age	*Mean ± SD*	33 ± 10	31 ± 12	0.13
Male Gender	*n (%)*	37 (31%)	196 (65%)	<0.001
Body Mass Index	*Mean ± SD*	20.8 ± 0.7	21.9 ± 5.7	0.001
FEV1 (% predicted)	*Mean ± SD*	50 ± 12	46 ± 23	0.016
FVC (% predicted)	*Mean ± SD*	73 ± 9	57 ± 24	<0.001
Use of rhDNase	*n (%)*	121 (100%)	303 (100%)	n/a
Sputum Positivity for Pseudomonas aeruginosa	*n (%)*	60 (50%)	211 (70%)	<0.001
Sputum Positivity for MRSA	*n (%)*	60 (50%)	97 (32%)	0.001
Airway clearance device (Chest Vest OR flutter valve)	*n (%)*	80 (93%)	143 (97%)	
Hospitalization / Home i.v. antibiotics	*n (%)*	41 (52%) / 41 (48%)	88 (60%) / 60(40%)	

FEV1 = Forced Expiratory Volume in one second

FVC = Forced Vital Capacity

rhDNase = Recombinant human DNase

MRSA = Methicillin-resistant Staphylococcus Aureus

Table 2. Odds ratios using inhaled hypertonic saline (*n*=99) for pulmonary exacerbations (*n*=340) using univariate analysis

Lung Disease Severity	Odds Ratio	Confidence Intervals		*p*-value
		Lower	Higher	
Mild (*n*=50)	0.09	0.01	0.812	**0.012**
Moderate (*n*=183)	1.33	0.65	2.74	0.432
Severe (*n*=170)	5.62	0.73	43.21	0.063

Table 3. Odds ratios using inhaled hypertonic saline (*n*=99) for pulmonary exacerbations (*n*=340) using multivariate analysis

Lung Disease Severity	Odds Ratio	Confidence Intervals		*p*-value
		Lower	Higher	
Mild (*n*=50)	0.17	0.05	0.58	**0.004**
Moderate (*n*=183)	0.39	0.16	0.93	**0.034**
Severe (*n*=170)	0.02	0.001	0.452	**0.015**

Discussion

Exacerbations of CF lung disease account for appreciable morbidity and burden of this disease, which collectively greatly decrease physical functioning and psychosocial quality of life.[7] Pulmonary exacerbations in particular significantly contribute to the overall cost of CF care, accounting for up to 47% of overall costs in one study.[8] Accordingly, measures to decrease pulmonary exacerbations are important. Inhaled HS decreases the viscosity of pulmonary secretions and thereby improves the rheologic properties of mucus secondary to hydration of the airway surface.[9] In addition, HS osmotically induces a sustained increase in the airway surface liquid volume depth, possibly allowing the cilia to beat freely by re-coupling the mucociliary mechanism.[10] Inhaled HS for CF lung disease is currently assigned a Grade II recommendation in the Cystic Fibrosis Pulmonary Guidelines published in 2007,[5] based on evidence from the above-cited trials.[2-4] Notably, in the trial reporting the efficacy of HS in reducing clinical exacerbations,[2] patients with severe CF lung disease (as classified by FEV_1 < 40% predicted) were excluded; moreover, only approximately one-third of the included participants were using nebulized rhDNase.

Here, we have assessed the effects of inhaled HS in reducing the number of pulmonary exacerbations across varying levels of lung disease severity, especially considering that more severe forms of CF lung disease had been previously excluded.[2] Our study suggests that inhaled HS is beneficial in reducing exacerbations across all stages of CF lung disease using multivariate analyses, even though univariate analysis only showed benefit in mild CF lung disease. These findings underscore the potential therapeutic benefit of initiating inhaled HS at any stage in the disease continuum. Our study group had a significantly higher usage of nebulized rhDNase (100%) and other mechanical airway clearance therapies (97%) compared to

previous studies.[2] Hence, we postulate that there may be additional benefit of inhaled HS in patients who are already on established airway clearance strategies. We also found no indication of any excessive discontinuation of inhaled HS due to cough or bronchospasm in more severe forms of CF lung disease, suggesting that it is reasonably well tolerated even in such cases.

Even so, the methodological limitations of our study must be acknowledged, principally its retrospective nature and lack of randomization. Mild exacerbations could possibly go unreported; moreover, there was no uniform protocol in place to assess compliance with therapy. Furthermore, the two study groups had differences in epidemiological characteristics, for e.g., the lower proportion of sputum Pseudomonas positivity in HS users, thereby potentially lending bias to our interpretation. In this context, regression analyses in an attempt to adjust for these variable clinical and epidemiological characteristics was performed. However, ultimately, prospective randomized controlled studies with larger numbers of included participants are warranted to better assess the benefit of inhaled HS at varying stages of CF lung disease severity.

Conclusion

Our study demonstrated that pulmonary exacerbations appear to be reduced in patients with CF lung disease of any severity during active use of inhaled HS. The beneficial effect of HS was additive to other airway clearance measures such as nebulized rhDNase and mechanical clearance strategies. Moreover, inhaled HS appeared reasonably well tolerated. Recently, the effectiveness of alternative therapies such as nebulized mannitol for mucociliary clearance has been reported.[11] Until these newer strategies are better established, we support the use of inhaled HS in CF lung disease, in the context of reducing pulmonary exacerbations. This is

especially so given the potential to improve lung function, quality of life, CF-related costs, and possibly mortality.[1, 7, 8, 12, 13]

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Competing Interests Statement: The authors of this study report no competing interests or financial disclosures.

Contributorship Statement

Dr. Dmello was involved in conception and design of the study, data analysis as well as authoring and revising the manuscript. Dr. Nayak and Dr. Matuschak were involved in the design of the study as well as in manuscript review. All authors have reviewed and approved the final version of the manuscript.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *case-control studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	*(*a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5,6
		(*b*) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how matching of cases and controls was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6,7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	6,7,9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	6,7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.