



N-AcetylCysteine, Hypertonic Saline and Mannitol in Chronic Respiratory Diseases; Efficiency and Safety Considerations

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Authors' contributions

This work was carried out in collaboration between all authors. Author MS managed the literature searches and designed the tables. Authors AT and MG did the critical revise of the article. All authors read and approved the final manuscript.

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ABSTRACT

Chronic Respiratory Diseases (CRDs) are a group of long-lasting malfunctions of respiratory system. Almost all of them, are not curable and pharmacological interventions are life-time. Because of the chronic use of therapies, safety of the interventions are as important as efficacy of them. According to the guidelines of therapy, inhaled corticosteroids, inhaled beta2-agonists, methylxanthines and phosphodiesterase inhibitors are main current agents for the treatment of CRDs, while there exists a wide range of adverse reactions during long-time use of the drugs. Adding efficient agents with less side effects could be beneficial. In this article we review the efficacy and safety profile of N-AcetylCysteine, Hypertonic Saline and Mannitol on different types of CRDs, and recommend their use in the management of CRDs.

Methods: All information was collected from articles of international medical journals and online

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databases using key words below. PubMed, Cochrane library, Scopus, Google Scholar, and Clinicaltrial.gov databases were searched for literature published between January 2000 and December 2015.

Conclusion: Adding these agents to first line of therapy for CRDs could be beneficial, while more studies are needed to support their use in clinical setting.

Keywords: Chronic respiratory disease; N-AcetylCysteine; hypertonic saline; mannitol.

1. INTRODUCTION

Chronic respiratory diseases (CRDs) are chronic diseases of the airways and other structures of the lung lasting for a long time, most of the time life-time. They are a group of diseases with some similar symptoms which affect the quality of life (QOL) of the patients. Several torturous symptoms include frequent coughs, abnormal sputum, difficulty in breathing and dyspnea, wheezing, frequent respiratory infections, shortness of breath and throat irritation [1,2].

Despite the therapeutic advances, these patients still have poor quality of lives. They are always under the influence of their disease and their lives is disturbed [3-5].

The pharmacotherapies being used were beneficial, but not curative enough. Also most of them have shown many different adverse effects which hurt the patients in long time.

In this article we are going to talk about three drugs which their beneficial effects in CRDs is under investigation: N-AcetylCysteine, Hypertonic Saline and Mannitol.

They have shown some significant helpful results in several studies for different CRDs, with least risk of possible adverse effects.

We recommend that these three can be added to guidelines of therapy for CRD patients, considering their much lower adverse effects.

2. METHODS

All information that have been used to write this review article are collected from articles of international medical journals and online databases published between January 2000 and December 2015. To access related studies, keywords such as Chronic Respiratory Disease, Lung Disease, COPD, Asthma, Chronic Bronchiolitis, Bronchiectasis, Mustard Gas, Inhaled Corticosteroids, N-AcetylCysteine,

Inhaled Hypertonic Saline and Inhaled Mannitol are used in PubMed, Cochrane library, Scopus, Google Scholar, and Clinicaltrial.gov databases.

2.1 Chronic Respiratory Diseases

Chronic respiratory diseases or diseases affecting respiratory system *for long periods of time* are a wide range of respiratory malfunctions with different pathophysiologies. Asthma, Bronchiectasis, Chronic Obstructive Pulmonary Disease (COPD), Chronic Rhinosinusitis, Lung fibrosis and Chronic Bronchitis are the most common CRDs in the world.

They are the major causes of patient's hospitalization along with cardiovascular diseases and stroke. According to WHO statistics published on 2012, COPD is the third leading cause of death in the world [6-8].

The latest estimation (2004) of WHO shows that more than 235 million people have asthma, 64 million people have chronic obstructive pulmonary disease (COPD) and millions of other chronic respiratory malfunctions [1].

Nowadays tobacco smoking and air pollution are two main factors that increase the rate of respiratory diseases in the world [9-11].

While different CRDs have different pathophysiologies and differential symptoms, there are many common life-time symptoms. Symptoms like difficulty in breathing and dyspnea, frequent coughs, wheezing, frequent respiratory infections, abnormal sputum, shortness of breath and throat irritation are seen in most of the CRD patients and lower the quality of life [12].

2.2 Pharmaco-therapy and Pharmaco-management of CRDs

2.2.1 Goals and objectives

There are some similar goals of therapy and managements in different CRDs [13-15]:

- Improving health status and quality of life
- Prevention and treating exacerbations
- Improving exercise tolerance
- Prevention from disease progression
- Improving lung function parameters (FEV1, FVC and ratio of them)
- Reducing the frequency of respiratory infections, coughs and shortness of breath
- Improvement in sputum condition
- Relieving other common symptoms

2.2.2 Routine pharmacologic therapies for chronic respiratory diseases

According to the guidelines of therapy of CRDs, inhaled Corticosteroids and beta2-agonists are the first choices of pharmacotherapy in approximately all types of CRD. Also antibiotics are being used to reduce and manage bacterial infections of the respiratory system because of recurrent lung infections in respiratory malfunctions. In addition methylxanthines and phosphodiesterase inhibitors are in 2nd line of therapy [16-19].

Long term use of these therapeutic agents have shown wide range of side effects, some of them serious and more harmful.

2.2.2.1 Inhaled corticosteroids side effects:

- Local adverse effects:

Pharyngitis, Dysphonia, Reflex cough, Bronchospasm, Oropharyngeal candidiasis

- Systemic side effects:

Suppressed HPA-axis function, Adrenal crisis (with insufficiency), Suppressed growth velocity in children, Decreased lower-leg length in children, Reduced bone mineral density, Suppressed HPA-axis function, Bone fractures, Osteoporosis, Skin thinning, Skin bruising, Cataracts, Glaucoma [20]

Also other common therapeutic agents in CRDs have shown some clinically important adverse effects.

While muscle cramps and muscle twisting were the most frequent side effects of Inhaled beta2-agonists, cardiovascular side effects, especially QT-Prolongation was the most serious.

Bronchitis, Nasal congestion, Influenza and Chest tightness are some harmful effects which worsen the patient's condition [21-23].

Theophylline with a narrow therapeutic index has several possible adverse effects:

Central nervous system excitement, Headache, Insomnia, Irritability, Restlessness, Seizure, Diarrhea, Nausea, Vomiting, Diuresis (transient), Exfoliative dermatitis, Skeletal muscle tremors, Tachycardia, Flutter, Acute myocardial infarction, Seizures (resistant to anticonvulsants), Urinary retention [24, 25].

Because of the wide range of adverse effects of pharmacologic agents prescribed in CRDs (three agents talked about above and also many others which are not mentioned) and the chronic life-time use of them, developing new methods of therapy with effective and less harmful agents seem to be beneficial and helpful. Thus, we here discuss three agents that can remedy different symptoms of CRDs with much lower side effects.

2.3 N-AcetylCysteine

N-AcetylCysteine is a mucolytic drug with considerable antioxidative properties; Both can be beneficial in CRDs. Excessive and thick mucus production is one of the most common symptoms of different types of CRDs, which could be relieved by NAC because of its mucolytic effect. Excess amounts of mucus can lead to problems in breathing, frequent coughs; frequent infections (sputum can be a source of food for bacteria) and some other symptoms; thus NAC with its mucolytic property can be a remedy for most of the symptoms pharmacologically. Also pathophysiological studies have shown that in many types of CRDs oxidative mechanisms are playing an important role, so antioxidant agent, NAC, can be helpful by reduction of oxidant toxics [26].

Almost all studies have shown good safety profile of chronic use of NAC and no major side effects were seen. Life-threatening and hazardous adverse drug reactions are rare [27, 28].

Some clinical trials that have evaluated NAC's effectiveness in CRDs. As shown in Table 1, many different symptoms are relieved and QOL is improved [29-37].

Table 1. Some clinical trials that have evaluated N-acetyl cysteine in chronic respiratory diseases [29-37]

#	Title	Disease	Intervention	Parameters studied	Results	Year of study	Reference
1	Therapeutics effect of N-acetyl cysteine on mustard gas exposed patients: Evaluating clinical aspect in patients with impaired pulmonary function test	Mustard gas exposed patients	600mg tid	1. Cough 2. Dyspnea 3. Wake-up dyspnea 4. Hemoptysis Pulmonary function tests (PFTs)	1. NAC was effective in reducing Cough, Dyspnea, Wake-up dyspnea and Hemoptysis 2. PFTs significantly improved.	2008	29
2	High-Dose N-Acetylcysteine in Stable COPD: The 1-Year, Double-Blind, Randomized, Placebo-Controlled HIACE Study	COPD	600mg bid	1. Lung function parameters 2. Modified Medical Research Council (mMRC) dyspnea 3. St. George's Respiratory Questionnaire (SGRQ) scores 4. 6-min walking distance (6MWD) 5. Exacerbation and admission rates	1. Significant improvement in forced expiratory flow 2. Significant reduction in exacerbation frequency 3. Reduction in admission rates	2013	30
3	High-Dose N-Acetylcysteine in Chronic Obstructive Pulmonary Disease, Prone Positioning in Acute Respiratory Distress Syndrome, and Continuous Positive Airway Pressure and Exhaled Nitric Oxide in Obstructive Sleep Apnea	COPD	600mg bid	1. Lung function parameters 2. frequency of exacerbation 3. hospitalization days 4. St. George's Respiratory Questionnaire score 5. mMRC 6. 6MWD	1. Decreased hospitalization days 2. improvement in FEF 3. reduced frequency of exacerbations 4. increased proportion of exacerbation-free participants	2014	31
4	Effect of N-Acetylcysteine on Air Trapping in COPD:A Randomized Placebo-Controlled Study	COPD	600mg bid	Pulmonary Function Tests at rest and after exercise	1. Higher IC and FVC especially after exercise 2. Decrease in the relationship of residual volume to total lung capacity 3. Increased endurance time 4. Beneficial effect on physical performance, due to a reduction in air trapping	2009	32

#	Title	Disease	Intervention	Parameters studied	Results	Year of study	Reference
5	N-Acetylcysteine Improves the Clinical Conditions of Mustard Gas-Exposed Patients with Normal Pulmonary Function Test	Mustard Gas Exposed Patients	NAC 1200 mg daily for 4 months	1. Dyspnea 2. Wake-up dyspnea 3. Cough 4. Sputum 5. PFTs	1. Dyspnea, wake-up dyspnea and cough improved 2. Sputum reduced 3. PFTs (FEV1, FVC and FEV1/FVC) improved	2008	33
6	Efficacy of oral long-term N-acetylcysteine in chronic bronchopulmonary disease: A meta-analysis of published double-blind, placebo-controlled clinical trials	Chronic Bronchitis	Meta-analysis: daily dose of 400 mg (1 study), 600 mg (5 studies), 1200 mg (1 study) and 600 mg 3 times per week	Acute exacerbations	a prolonged course of oral NAC prevents acute exacerbations of CB	2000	34
7	N-acetylcysteine inhibit biofilms produced by <i>Pseudomonas aeruginosa</i>	<i>P.aeruginosa</i> biofilms (<i>Pseudomonas aeruginosa</i> is a common pathogen in chronic respiratory tract infections.)	Adding NAC to Ciprofloxacin	1. PAO1 biofilm biomass and its heterogeneity 2. viable biofilm-associated bacteria 3. Extracellular polysaccharides (EPS) production by <i>P. aeruginosa</i>	1. PAO1 biofilm biomass decreased and its heterogeneity increased 2. Viable biofilm-associated bacteria decreased 3. Extracellular polysaccharides (EPS) production by <i>P. aeruginosa</i> decreased So NAC has anti-bacterial properties against P.A.	2010	35
8	High-dose oral N-acetylcysteine, a glutathione prodrug, modulates inflammation in cystic fibrosis	Cystic Fibrosis (CF)	600-1000mg tid	1. Blood neutrophils 2. Sputum elastase activity 3. Sputum IL-8 levels	1. Blood neutrophils deficiency was improved 2. Decreased sputum elastase activity 3. Decreased sputum IL-8 levels So high-dose oral N-acetylcysteine improves redox and inflammatory imbalances in CF	2006	36
9	High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis	Pulmonary Fibrosis	600mg tid	1. Vital capacity 2. Diffusing capacity of the lungs for carbon monoxide (DLCO)	Acetylcysteine slowed the deterioration of vital capacity and DLCO	2005	37

Table 2. Some clinical trials that have evaluated *Hypertonic Saline* in chronic respiratory diseases [42-49]

#	Title	Disease	Intervention	Parameters studied	Results	Year of study	Reference
1	Nebulized hypertonic saline decreases IL-8 in sputum of patients with cystic fibrosis	Cystic fibrosis	Nebulization of HTS (7% saline)	1. IL-8 in CF lung secretions 2. Neutrophil chemotactic efficiency	1. Degradation of IL-8 2. Decreased neutrophil chemotactic efficiency	2011	42
2	A Controlled Trial of Long-Term Inhaled Hypertonic Saline in Patients with Cystic Fibrosis	Cystic Fibrosis	Inhale 4 ml of either 7 percent hypertonic saline or 0.9 percent (control) saline twice daily for 48 weeks	1. PFT 2. Pulmonary exacerbations 3. Bacterial infection or inflammation	1. Significantly higher FVC and FEV1 2. Significantly fewer pulmonary exacerbations 3. Significantly higher percentage of patients without exacerbations Hypertonic saline was not associated with worsening bacterial infection or inflammation	2006	43
3	Mucus Clearance and Lung Function in Cystic Fibrosis with Hypertonic Saline	Cystic Fibrosis	Inhaled hypertonic saline (5 ml of 7 percent sodium chloride) four times daily, 14 days	1. Mucus Clearance 2. PFTs (FEV1 and FVC)	1. Acceleration of mucus clearance 2. Improvement in FEV1 and FVC	2006	44
4	Evaluation of nebulized hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis	Bronchiectasis	Adding nebulized hypertonic saline (7%) to treatment schedules	1. PFTs 2. Sputum viscosity 3. Sputum weights 4. Ease of expectoration	1. Improved FEV1 and FVC 2. Reduced sputum viscosity 3. Higher Sputum weights	2005	45
5	Nebulized 7% hypertonic saline improves lung function and quality of life in bronchiectasis	Bronchiectasis	HS or IS daily for 3 months	1. PFTs 2. Quality of life 3. Health care utilization responses	1. Better FEV1 and FVC with HS vs IS 2. St. George's Respiratory Questionnaire improved with HS 3. Reductions in annualized antibiotic usage specially with HS 4. Reductions in annualized emergency health care utilization visits with HS 5. Improvements in sputum viscosity and ease of expectoration	2011	46
6	Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants	Viral Bronchiolitis	Repeated doses of nebulized 3% HS in addition to routine therapy	Hospital length of stay (LOS)	Clinically significant reduction in LOS	2007	47
7	Safety of sputum induction	COPD	Adding nebulized HS to routine	1. PFTs	No severe adverse effects, So it is	2007	48

#	Title	Disease	Intervention	Parameters studied	Results	Year of study	Reference
	during exacerbations of COPD		management of COPD exacerbations	2. Sputum samples	considered to be safe		
8	The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis	Bronchiectasis	Patients were randomized to inhale isotonic saline (IS) 0.9% or HTS 6% daily for 12 months	1. Quality of life 2. PFTs 3. Number of exacerbations 4. Changes in sputum colonization	All four parameters improved after adding HS and IS to the treatment	2012	49

Table 3. Some clinical trials that have evaluated *Mannitol* in chronic respiratory diseases [52-59]

#	Title	Disease	Intervention	Parameters studied	Results	Year of study	Reference
1	Inhaled mannitol improves lung function in cystic fibrosis	Cystic Fibrosis	Inhaled 420 mg bid	PFTs (FEV1, FVC)	Significantly improved lung functions. Safety and efficacy approved.	2008	52
2	Inhaled mannitol for the treatment of mucociliary dysfunction in patients with bronchiectasis: effect on lung function, health status and sputum	Bronchiectasis	Inhaled 400 mg once daily	1. Health status using the St George's Respiratory Questionnaire (SGRQ) 2. Viscosity, elasticity, spinnability, surface tension, contact angle, solids, mucociliary transportability (MCTR) and cough transportability (CTR) of Sputum 3. PFTs (FEV1, FVC)	1. Significantly improved the health status 2. Reduced tenacity of mucus 3. Increased hydration of mucus 4. Improved cough clearability	2005	53
3	Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomized, controlled trial	Bronchiectasis	Inhaled 400 mg bid	1. Exacerbation rates 2. Time to first exacerbation 3. Quality of life (QOL) (St George's Respiratory Questionnaire, SGRQ).	1. Significant improvements in Time to first exacerbation 2. QOL Significantly improved	2014	54
4	The 24-h effect of mannitol on the clearance of mucus in patients with bronchiectasis	Bronchiectasis	Inhaled 330 mg only on day 2	1. Retention of mucus 2. PFTs (FEV1, FVC)	1. 24-h retention of mucus reduced 2. Clearance of mucus increased acutely	2001	55

#	Title	Disease	Intervention	Parameters studied	Results	Year of study	Reference
5	Inhaled mannitol changes the sputum properties in asthmatics with mucus hypersecretion	Asthma	635 mg (Visit 1), 240 mg (Visit 2), 360 mg (Visit 3) and 360 mg in the presence of montelukast (Visit 4)	Viscoelasticity, surface tension, contact angle and the solids content of sputum	Reduction in viscoelasticity, surface tension, contact angle and the solids content of sputum	2007	56
6	Inhaled Mannitol Improves the Hydration and Surface Properties of Sputum in Patients With Cystic Fibrosis	Cystic Fibrosis	420 mg bid	1. Solids 2. Surface tension 3. Contact angle 4. Viscoelastic properties of sputum 5. Pulmonary function tests	1. Reduced solids, surface tension and contact angle 2. PFTs improvement	2010	57
7	Long-Term Inhaled Dry Powder Mannitol in Cystic Fibrosis	Cystic Fibrosis	400mg bid	1. PFTs 2. Pulmonary exacerbation 3. Hospitalization 4. Sputum microbiology	1. Improved PFTs 2. Reduction in exacerbation rates and hospitalization	2012	58
8	Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study	Cystic Fibrosis	400mg bid	1. PFTs 2. Pulmonary exacerbation	1. Improved PFTs 2. Reduction in exacerbation rates	2011	59

2.4 Hypertonic Saline

Hypertonic saline (HTS) is a hypertonic sterile solution of salty water that can be inhaled as a nebulized medication.

Multiple mechanisms of action have been found for the beneficial effects of HTS in CRDs.

Osmotic pressure made by HTS adds water to the airway surface; Thus makes the rheological properties of the mucus more favorable for clearance. HTS also triggers cough reaction and the cough increases the amount of mucus cleared from lungs. Disrupting ionic bonds within the mucus gel by HTS reduces its viscosity and elasticity because of the reduction of cross-linkings. Also, anti-inflammatory effects have been seen by HTS. It has been shown that hypertonic saline reduces biofilm formation by micro-organisms. HTS has anti-oxidative properties by increasing the level of thiols [38, 39].

According to different studies, nebulized HTS is well tolerated in patients and no severe ADR is common. [40] Cough and chest tightness are the most common causes make patients unable to tolerate HTS. [41]

Some clinical trials that have evaluated HTS's effectiveness in CRDs is shown in Table 2. As can be seen in the table, many different symptoms are relieved and QOL is improved [42-49].

2.5 Mannitol

Mannitol is a sugar alcohol with a wide range of therapeutic uses. It can be inhaled as a nebulized medication in CRDs.

The same with hypertonic saline it acts as a mucoactive agent and hydrates the airways because of the osmotic gradient, thus remedies some of the symptoms of CRDs [50-52].

No serious ADR is observed in different studies with inhaled Mannitol and safety of chronic use of it is shown [52, 54].

Some clinical trials that have evaluated Mannitol's effectiveness in CRDs is shown in Table 3. As can be seen in the table, many different symptoms are relieved and QOL is improved [52-59].

3. DISCUSSION

Low quality of life because of frequent coughs, abnormal sputum, dyspnea, wheezing, shortness of breath, throat irritation, etc. is seen in CRDs. Patients suffer from these symptoms and their lives is disturbed.

Previous studies have shown wide range of beneficial effects of N-AcetylCysteine, Hypertonic saline and Mannitol which can significantly improve QOL. Reduction in Cough, Dyspnea, Wake-up dyspnea, Hemoptysis and exacerbation frequency, physical performance improvement, reduction in admission rates and hospitalization days, reduced respiratory infections frequency and many other helpful effects have been seen by NAC. HTS and Mannitol decreased exacerbation frequency, admission rates and hospitalization days. Sputum condition was improved and expectoration was eased by them. Also improved quality of life (QOL) is reported by NAC, HTS and Mannitol according to the improved St. George's Respiratory Questionnaire (SGRQ) index.

The importance of safety and low rates of adverse drug reactions in therapy of chronic and long-lasting diseases like CRDs is obvious; because of the lifetime interventions. Reduction in frequency and doses of agents with more side effects by replacing them by agents with lower side effects could be beneficial. NAC, HTS and Mannitol seem to have less ADRs than routine pharmacotherapies for CRDs. Knowledge of chronic use of these agents as inhaled formulations is lacking and more studies are needed to explore these agents as a first line of therapy for CRDs. Large-scale clinical trials could evaluate the possibility of replacing routine pharmacologic agents of guidelines by them.

4. CONCLUSION

In summation, increasing data support the use of NAC, HTS and Mannitol in CRDs considering their efficiency and safety. Further studies are needed to evaluate the long-term efficiency and safety of them as an adjuvant or monotherapy. Also, studying on novel formulations and different particle shapes and particle sizes of these agents and comparison of them with standard therapies seems to be advantageous.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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