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Airway Clearance in Bronchiectasis: A Randomized Control Trial with N-Acetylcysteine and 3% Hypertonic Saline

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ABSTRACT

Background: N-Acetylcysteine and 3% hypertonic saline are being used effectively for sputum clearance in chronic cases of bronchiectasis for quite some time. However, their use in acute condition of the disease seems to be underexplored. The objective of our study is to compare the role of nebulized N-acetylcysteine and 3% hypertonic saline in clearing the airway in patients with acute exacerbation of bronchiectasis.

Material and Methods: A total of 136 confirmed cases of bronchiectasis were enrolled in this study. This randomized controlled trial was done in chest ward of Nishtar Hospital Multan from January 2015 to March 2017. Sampling was done by non-probability consecutive sampling and patients were divided into two groups A and B by lottery method. Verbal informed consent was taken from all participants. Group A participants received nebulization of N acetylcysteine mixed in normal saline for ten minutes, while group B participants were nebulized with 10ml of 3% hypertonic saline for ten minutes. Group B was active control group in the study. Data was collected on pre-designed Proforma, and analyzed by SPSS version 22. Numerical variables such as saturation, weight of sputum, age and blood pressure was analyzed by using t test. These were considered significant if the p value was equal or less than 0.05. For qualitative variables chi square test was applied.

Results: The mean O₂ saturation of Group A, before and after treatment, was 92.11±3.07% and 94.47±2.18%, respectively. The difference was statistically significant (p value =0.001). The sputum weight of Group A, before and after treatment, was 2.63±2.39 g and 7.41±1.38 g, respectively. The difference was statistically significant (p value =0.001). The frequency of rhonchi of Group A, before and after treatment, was 52% and 76%, respectively. The difference was statistically significant (p value =0.003). While, for Group B, the mean O₂ saturation, before and after treatment, was 92.36±3.13% and 93.49±2.27%, respectively. The difference was statistically significant (p value =0.012). The sputum weight, before and after treatment, was 3.11±2.01 g and 5.56±1.02 g, respectively. The frequency of rhonchi, before and after treatment, was 45% and 74% respectively. Again, the difference was statistically significant.

Conclusion: Both nebulized N-acetylcysteine and 3% hypertonic saline cause airway clearance by enhancing sputum expectoration in patients with acute exacerbation of bronchiectasis equally. Both these agents also improve oxygen saturation in acute exacerbation of bronchiectasis significantly.

Key words: Bronchiectasis, Hypertonic saline, N-acetylcysteine

Authors' Contribution:

^{1,2} Conception, synthesis, planning of research and manuscript writing
Interpretation, discussion, ^{3,4} Active participations in data collection
⁵ Data analysis.

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Introduction

N-Acetylcysteine is a mucolator and a drug with antioxidant qualities. Both these qualities make it suitable for the treatment of chronic respiratory diseases, because there is excessive production of thick mucus. Large amount of mucus production causes repeated infections, difficulty in breathing, excessive cough and other symptoms, and this can be treated with mucolator qualities of N-acetylcysteine. Oxidative process has a major role in pathophysiology of many chronic respiratory diseases, and N-acetylcysteine reduces oxidant toxins.¹ Long term use of N-acetylcysteine has good safety profile with no major side effects. Serious side effects are very rare.^{2,3} In many chronic respiratory diseases, clinical trials of N-acetylcysteine have been carried out and results have shown that it relieved symptoms and improved quality of life.^{4,5}

Hypertonic saline is salty water and is found to be beneficial when nebulized in many chronic respiratory diseases. It has various mechanisms of action; it produces osmotic pressure which causes addition of water to surface of airway and this rheological quality makes the mucus suitable for clearance through cough. It also causes disruption of bond in mucus gel and thus reduces viscosity and elasticity by reducing cross linking. It is said to have shown some anti-inflammatory properties as well by reducing the formation of bio-film by organisms. Hypertonic saline increases the levels of thiols and behaves as anti-oxidants.^{6,7} In nebulized form, it is well tolerated and no adverse reactions are reported.⁸ In many chronic respiratory diseases, efficacy of hypertonic saline has been evaluated and is said to have shown improvement in quality of life by relieving symptoms.^{9,10}

Although the role of both these agents is well established in clearing airway during chronic bronchiectasis, but their action in acute exacerbation of the same disease seems to be underexplored. To the best of our knowledge no study has been carried out in this regard so far. Therefore, we compared the efficacy of both N-Acetylcysteine and 3% hypertonic solution in clearing the airways in acute exacerbation of the disease and hope to provide some evidence-based data regarding their usefulness.

Material and Methods

After approval from Ethical Committee of Nishtar Hospital Multan, a total of 136 participants were recruited for the study. All the participants were diagnosed cases of acute exacerbation of bronchiectasis and were admitted in the Chest Ward of Nishtar Hospital Multan from January 2015 to March 2017 either through Emergency or Outpatient Departments. Acute exacerbation of bronchiectasis was defined as worsening of shortness of breath, fever or increased production of sputum. Sample size was calculated by taking a reference study with power of study 80 and confidence interval 95% in which sputum expectoration was 2.65 ± 3.47 g and after treatment was 7.5 ± 6.29 g by using software www.openepi.com.¹¹

Sampling was done by non-probability consecutive sampling and patients were divided into two groups A and B by lottery method. Verbal informed consent was obtained from all participants of the study. Group A were given standard medical treatment for bronchiectasis with nebulization of N acetylcysteine mixed in normal saline for ten minutes while group B participants were nebulized with 10ml of 3% hypertonic saline also for ten minutes. Group B in the study was considered as active control group.

A focused history was taken from all the patients and detailed examination was done. The demographic information and the variables to be studied were recorded by the investigators on self-designed proforma. Demographic variables included age, gender, blood pressure, smoking status, educational status, residential area and diabetes.

Chest was auscultated for wheeze, or rhonchi and findings were recorded. Blood samples were drawn and baseline investigations were done. Forty minutes before nebulization sputum samples were collected from every patient and their weight recorded. After that nebulization with assigned drug was started for each patient in both the groups. Patients of both groups were nebulized three times in 24 hours. After 24 hours, sputum was collected again in calibrated containers and its weight measured. Oxygen saturation was also measured.

Data was analyzed by SPSS version 22. Numerical variables such as age, blood pressure, saturation, weight of sputum, were analyzed by t-test. These were considered significant if the p value was equal or less than 0.05. Percentages of qualitative variables were calculated and chi square test was applied to test their significance.

Results

Table I presents the details of demographic data. There were more males affected by the acute exacerbation than females and more patients belonged to rural than urban areas. The percentage of smokers was greater in group A and those of non-smokers was greater in group B. Comparison of parameters pre- and post-nebulization is shown in Table II. Oxygen saturation improved after nebulization in both the groups (A and B) as apparent by the statistically significant difference of 0.001 and 0.012 respectively.

Sputum weight also increased after nebulization in both the groups significantly with p value of 0.001 in both the groups. Similar is the case with frequency of rhonchi which increased after nebulization with both the drugs significantly with p value of 0.003 and 0.001 in groups A and B respectively.

Variables	Group A n=68	Group B n=68
Mean Age (years)	38.89±2.57	46.07±5.12
Mean Blood pressure (mm Hg)	91.13±1.11	96.48±2.26
Gender n (%)		
Male	37 (54.4%)	47 (69.1%)
Female	31 (45.6%)	21 (30.9%)
Smoking n (%)		
Yes	38 (55.9%)	27 (39.7%)
No	30 (44.1%)	41 (60.3%)
Education Status n (%)		
Literate	41 (60.3%)	32 (47.1%)
Illiterate	27 (39.7%)	36 (52.9%)
Residential area n (%)		
Rural	47 (69.1%)	41 (60.3%)
Urban	21 (30.9%)	27 (39.7%)
Diabetics n (%)		
	15 (22.1%)	10 (14.7%)

Variable	Before Treatment	After Treatment	P-value
Oxygen saturation (%)			
Group A	92.11±3.07	94.47±2.18	0.001
Group B	92.36±3.13	93.49±2.27	0.012
Sputum weight (g)			
Group A	2.63±2.39	7.41±1.38	0.001
Group B	3.11±2.01	5.56±1.02	0.001
Ronchi (%)			
Group A	52%	76%	0.003
Group B	45%	74%	0.001

Discussion

Patients of both groups showed significant improvement after nebulization three times in 24 hours. Patients in both groups expectorated significantly greater amount of sputum post-nebulization thus improving symptoms. Effects of N-acetylcysteine in clearing airway and sputum expectoration have been observed in various studies. Outcomes of our study are consistent with most of the other researches. Hirsch and Kory demonstrated that nebulization with N-acetylcysteine caused thinning of sputum leading to increased expectoration.¹² Kory et al reported increase sputum expectoration when N-acetylcysteine was combined with a bronchodilator in patients with chronic bronchitis.¹³ Pavia et al reported significantly improved sputum expectoration after nebulization with hypertonic saline of 7.1%.¹⁴ However, N-acetylcysteine when used in nebulization form for mechanically ventilated patients did not lead to significant improvement in airway clearance.¹⁵

Improved airway clearance by mucolytic agents caused improved lung function and oxygen saturation by improving minimizing effects of atelectasis. Ueno O. et al demonstrated that nebulization of N-acetylcysteine in obstructive lung disease caused improved oxygenation and hypercapnia was relieved. N-acetylcysteine also caused improved gaseous exchange after bronchospasm caused by methacholine challenge test.¹⁶ Hypertonic salines can be used to clear the airway by causing more hydration of the airway and electrostatic effects on respiratory secretions and also due to enhancing cough reflex and improved oxygenation.¹⁷

In a retrospective study, nebulization with hypertonic saline was used to treat acute exacerbation of cystic fibrosis, after which it caused bronchospasm.¹⁸ In a study by Pappová et al showed that nebulization with N-acetylcysteine caused bronchospasm by increasing airway reactivity.¹⁹ Similarly, in our study nebulization with both 3% hypertonic saline and N-acetylcysteine caused increased airway reactivity and rhonchi. We recommend further research in this regard. Limitations of the study were reduced sample size, one-center trial and no follow up after discharge.

Conclusion

Nebulization with both N-acetylcysteine and 3% hypertonic saline improves airway clearance by enhancing sputum expectoration in patients with acute exacerbation of bronchiectasis. Both these agents improve/increase oxygen saturation and post expectoration weight of sputum significantly.

References

1. Rushworth GF, Megson IL. Existing and potential therapeutic uses for N-acetylcysteine: the need for conversion to intracellular glutathione for antioxidant benefits. *Pharmacol Ther.* 2014; 141(2): 150-9. Doi: 10.1016/j.pharmthera.2013.09.006
2. Kranzer K, Elamin WF, Cox H, Seddon JA, Ford N, Drobniewski F. A systematic review and meta-analysis of the efficacy and safety of N-acetylcysteine in preventing aminoglycoside-induced ototoxicity: implications for the treatment of multidrug-resistant TB. *Thorax.* 2015; 70(11): 1070-7. Doi: 10.1136/thoraxjnl-2015-207245
3. Dodd S, Dean O, Copolov DL, Malhi GS, Berk M. N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility. *Expert Opin Biol Ther.* 2008; 8(12): 1955-62. Doi: 10.1517/14728220802517901
4. Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, et al. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. *Lancet Respir Med.* 2014 Mar;2(3):187-94.
5. Pirabbasi E, Shahar S, Manaf ZA, Rajab NF, Manap RA. Efficacy of ascorbic acid (vitamin C) and N-acetylcysteine (NAC) supplementation on nutritional and antioxidant status of male chronic obstructive pulmonary disease (COPD) patients. *J Nutr Sci Vitaminol (Tokyo).* 2016; 62(1): 54-61. Doi: 10.3177/jnsv.62.54
6. Jantrawut P, Phongpradist R, Muller M, Viernstein H. Enhancement of anti-inflammatory activity of polyphenolic flavonoid rutin by encapsulation. *Pak J Pharm Sci.* 2017; 30(5): 1521-1527. PMID: 29084668
7. Bedreag OH, Rogobete AF, Sarandan M, Cradigati AC, Papurica M, et al. Oxidative stress in severe pulmonary trauma in critical ill patients. Antioxidant therapy in patients with multiple trauma—a review. *Anaesthesiol Intensive Ther.* 2015; 47(4): 351-9. Doi: 10.5603/AIT.a2015.0030
8. Reeves EP, Williamson M, O'Neill SJ, Grealley P, McElvaney NG. Nebulized hypertonic saline decreases IL-8 in sputum of patients with cystic fibrosis. *Am J Respir Crit Care Med.* 2011; 183(11): 1517-23. Doi: 10.1164/rccm.201101-0072OC
9. Ros M, Casciaro R, Lucca F, Troiani P, Salonini E, Favilli F, et al. Hyaluronic acid improves the tolerability of hypertonic saline in the chronic treatment of cystic fibrosis patients: a multicenter, randomized, controlled clinical trial. *J Aerosol Med Pulm Drug Deliv.* 2014; 27(2): 133-7. Doi: 10.1089/jamp.2012.1034
10. Baron J, El-Chaar G. Hypertonic saline for the treatment of bronchiolitis in infants and young children: A critical review of the literature. *J Pediatr Pharmacol Ther.* 2016; 21(1): 7-26. Doi: 10.5863/1551-6776-21.1.7
11. Gallon AM. Evaluation of nebulised acetylcysteine and normal saline in the treatment of sputum retention following thoracotomy. *Thorax.* 1996; 51(4): 429-32. Doi: 10.1136/thx.51.4.429
12. Hirsch SR, Kory RC. An evaluation of the effect of nebulized N-acetylcysteine on sputum consistency. *J Allergy.* 1967; 39: 265-73. Doi: 10.1016/0021-8707(67)90090-1
13. Kory RC, Hirsch SR, Giraldo J. Nebulization of N-acetylcysteine combined with a bronchodilator in patients with chronic bronchitis. A controlled study. *Dis Chest.* 1968; 54: 504-9. Doi: 10.1378/chest.54.6.504
14. Pavia D, Sutton PP, Lopez-Vidriero MT, Newman SP, Clarke SW. Drug effects on mucociliary function. *Eur J Respir Dis* 1983; 64(Suppl 128): 304-17. PMID: 6137400

15. Masoompour SM, Anushiravani A, Norouz AT. Evaluation of the effect of nebulized N-acetylcysteine on respiratory secretions in mechanically ventilated patients: randomized clinical trial. *Iran J Med Sci.* 2015; 40(4): 309–315. PMID: 26170516
16. Ueno O, Lee LN, Wagner PD. Effect of N-acetylcysteine on gas exchange after methacholine challenge and isoprenaline inhalation in the dog. *Eur Respir J.* 1989; 2(3): 238-46. PMID: 2659384
17. Donaldson SH, Bennett WD, Zeman KL, Knowles MR, Tarran R, Boucher RC. Mucus clearance and lung function in cystic fibrosis with hypertonic saline. *N Engl J Med.* 2006; 354(3): 241-50. Doi: 10.1056/NEJMoa043891
18. Pezzulo AA, Stoltz DA, Hornick DB, Durairaj L. Inhaled hypertonic saline in adults hospitalised for exacerbation of cystic fibrosis lung disease: a retrospective study. *BMJ open.* 2012; 2(2): e000407. Doi: 10.1136/bmjopen-2011-000407
19. Pappová L, Kazimierová I, Kocmálová M. Effect of inhaled and oral n-acetylcysteine on airway defense mechanism. *Eur Pharmaceut J.* 2017; 64(1): 17-21. Doi: 10.1515/afpuc-2017-0002.