Acetylcysteine in the treatment of subacute sinusitis: A double-blind placebo-controlled clinical trial

Mehrzad Bahtouee, MD; Gholamhosein Monavarsadegh, MD; Mohammadjavad Ahmadipour, MD; Mazyar Motieilangroodi, MD; Niloofar Motamed, MD; Jamshid Saberifard, MD; Seyyedsajjad Eghbali, MD; Hooman Adibi, MD; Hesam Maneshi, MD ; Hasan Malekizadeh, MD

Abstract

Sinusitis is a common disease with harmful effects on the health and finances of patients and the economy of the community. It is easily treated in most of its acute stages but is associated with some management difficulties as it goes toward chronicity. Therefore, we tried to improve the treatment of subacute sinusitis by using acetylcysteine, which is a safe mucolytic and antioxidant agent. Thirty-nine adult patients with subacute sinusitis proved by computed tomography (CT) were enrolled in a double-blind, placebo-controlled trial. They received oral amoxicillin-clavulanic acid and normal saline nasal drops for 10 days and oral pseudoephedrine for 7 days. In addition, the patients received acetylcysteine (600 mg orally, once daily) in the intervention group or placebo in the control group for 10 days. A paranasal CT scan was taken at baseline and 30 days after patients finished the treatment and was evaluated quantitatively by Lund-Mackay (LM) score. Symptoms and some aspects of quality of life also were assessed at baseline and 14 days after initiation and 30 days after termination of the treatment via the Sino-Nasal Outcome Test questionnaire. The groups showed no significant difference in LM score after treatment. A positive correlation was observed between the LM and SNOT-20 scores. We concluded that adding oral acetylcysteine to amoxicillin-clavulanic acid, pseudoephedrine, and intranasal normal saline has no benefit for the treatment of subacute sinusitis.

From the Department of Internal Medicine (Dr. Bahtouee, Dr. Monavarsadegh, and Dr. Malekizadeh), the Department of Otolaryngology (Dr. Ahmadipour, Dr. Motieilangroodi, and Dr. Adibi), the Department of Public Health (Dr. Motamed), the Department of Radiology (Dr. Saberifard), and the Department of Pathology (Dr. Eghbali), Bushehr University of Medical Sciences, Bushehr, Iran; and the Department of Internal Medicine, Fasa University of Medical Sciences, Fasa, Iran (Dr. Maneshi).

Corresponding author: Mehrzad Bahtouee, MD, Department of Internal Medicine, Persian Gulf Martyr's Hospital, Azadi Square, Bushehr, Bushehr Province, Iran 7517933755. Email: bahtoueem@bpums.ac.ir

Introduction

Sinusitis is a common disease with potentially significant complications if left untreated.[1] These consequences increase as the course of the disease is prolonged. Medical management is successful in most patients with acute sinusitis, but it fails in some when they go toward the chronic form, which is difficult to treat and sometimes needs surgical intervention.

A group of patients whose disease was prolonged and was becoming chronic, but was subacute at the time of this study, were selected. Thereafter, the efficacy of acetylcysteine in the treatment of subacute sinusitis, defined as sinusitis lasting more than 3 weeks but less than 3 months, was examined.

Acetylcysteine is a medication with mucolytic and antioxidant effects that theoretically can help in the treatment of sinusitis by increasing drainage of secretions, improving mucosal protection during oxidative inflammatory processes,[2] inhibiting adhesion of microorganisms to epithelial cells,[3] and improving mucociliary clearance.[4] It is used in some diseases involving the respiratory tract and other organs, such as chronic obstructive pulmonary disease, the common cold, influenza, sinusitis, and contrast-induced nephropathy, and has few reported side effects.

We hypothesized that adding oral acetylcysteine to a commonly used treatment containing oral amoxicillin-

clavulanic acid, pseudoephedrine, and intranasal normal saline might increase improvement and prevent the disease from becoming chronic and therefore avoid high morbidities and difficulties in treatment.

Patients and methods

We collected our cases from outpatient clinics of Bushehr Medical University during a 4-month period lasting from autumn 2008 to spring 2009. Informed consent was obtained from all participants before they were enrolled in the study. A total of 103 patients with a clinical diagnosis of subacute sinusitis entered the study; of these, 76 remained after applying exclusion criteria (table 1).

Paranasal computed tomography (PNS-CT) in coronal and axial views was performed for all patients and was reviewed by our radiologist. Sinus opacification was reported in 58 cases, and the extent of sinusitis in each of 10 paranasal sinuses was calculated using the Lund-Mackay (LM) scoring system, which considers opacification of each sinus as none = 0, mild = 1, moderate = 2, marked = 3, and total = 4. In addition, occlusion of the ostiomeatal complex on each side was considered and reported as not occluded (0) or occluded (2). Thirteen patients refused to continue the study at this stage; the 45 remaining patients were randomly allocated to the intervention or the control group. All the involved physicians, assistants, analyzers, and patients were blind to group allocation.

At the beginning of the study, the patients completed the Sino-Nasal Outcome Test (SNOT-20) questionnaire, which addresses impairment of quality of life and common symptoms of sinusitis as follows: need to blow, sneezing, runny nose, cough, postnasal discharge, thick nasal discharge, ear fullness, dizziness, ear pain, facial pain/pressure, difficulty falling asleep, waking up at night, lack of a good night's sleep, waking up tired, fatigue, reduced productivity, reduced concentration, frustration, restlessness, irritability, sadness, and embarrassment. Each item is scored as no problem = 0, very mild problem = 1, mild or slight problem = 2, moderate problem = 3, severe problem = 4, or problem as bad as it can be = 5.

Next, patients in both groups received oral amoxicillin-clavulanic acid tabs (500 mg/125 mg every 8 hours) and normal saline nasal drops (3 drops every 4 hours) for 10 days and oral pseudoephedrine (60 mg every 6 hours) for 7 days. The patients in the intervention group also received acetylcysteine in the form of oral N-acetylcysteine (600 mg effervescent tabs once daily) for 10 days, and those in the control group received placebo.

We visited the patients 14 days after initiation of treatment. Six patients were lost to follow-up at that time; the remaining 39 patients completed the follow-up SNOT-20 questionnaire to assess improvement of symptoms after treatment. This visit was repeated 1 month after termination of treatment, at which time all

Table 1. Exclusion criteria

Allergic rhinitis	Nasal structural deformity found in Down syndrome	Hypertension
Severe asthma	Recent nasogastric tube	Hypotension
Pregnancy	Recent nasal packing	Benzodiazepine use
Diabetes mellitus	Tonsillar hypertrophy	Antidepressant use
Organ transplantation	Adenoid hypertropy	MAO-inhibitor, methyldopa, propranolol use
Chronic renal failure	Cleft palate	Warfarin use
Chemotherapy	Wegener granulomatosis	Age <18 years
Chronic alcoholism	Lupus erythematosus	Age >60 years
Severe malnutrition	Sarcoidosis	Dissatisfaction with participation in project
HIV positivity	Sjögren syndrome	Renal stone, especially cysteine and calcium
IV drug abuse	Churg-Strauss syndrome	Pilots
Steroid use	Cystic fibrosis	Divers
Heavy smoking	Kartagener syndrome	Sensitivity to penicillin
Severe septal deviation	Migraine headache	Sensitivity to N-acetylcysteine
Nasal polyposis	Cluster headache	Previous liver disorder
Nasal tumor	Benign prostatic hypertrophy	

Table 2. Sinus involvement in the intervention group before treatment (n = 18)

Sinus	None n (%)	Mild n (%)	Moderate n (%)	Marked n (%)	Complete n (%)
Right frontal	11 (61.1)	3 (16.7)	1 (5.6)	2 (11.1)	1 (5.6)
Left frontal	9 (50.0)	3 (16.7)	1 (5.6)	4 (22.2)	1 (5.6)
Right maxillary	3 (16.7)	3 (16.7)	6 (33.3)	4 (22.2)	2 (11.1)
Left maxillary	3 (16.7)	3 (16.7)	7 (38.9)	4 (22.2)	1 (5.6)
Right anterior ethmoidal	7 (38.9)	4 (22.2)	1 (5.6)	2 (11.1)	4 (22.2)
Left anterior ethmoidal	9 (50.0)	2 (11.1)	3 (16.7)	2 (11.1)	2 (11.1)
Right posterior ethmoidal	7 (38.9)	1 (5.6)	4 (22.2)	2 (11.1)	4 (22.2)
Left posterior ethmoidal	10 (55.6)	1 (5.6)	1 (5.6)	2 (11.1)	4 (22.2)
Right sphenoidal	17 (94.4)	1 (5.6)	0	0	0
Left sphenoidal	15 (83.3)	3 (16.7)	0	0	0

patients completed the follow-up SNOT-20 form and underwent another PNS-CT scan.

Data analysis was done with the Statistical Package for the Social Sciences version 11.5, using means and 95% confidence intervals, repeated measure analysis of variance, the paired *t* test, Pearson correlation coefficient, and the Mann-Whitney *U* and Wilcoxon tests.

Results

Of the 39 patients who completed the study, including follow-up, there were 18 patients (46.2%) in the intervention group and 21 (53.8%) in the placebo-control group. The mean age in these groups was and 30.5 years and 33.8 years, respectively. The extent of sinusitis before treatment is shown in tables 2 and 3.

At the beginning of treatment, the mean LM score was 13 (SD ± 9.36) in the intervention and 11 (SD ± 7.9) in the placebo group, indicating a similarity of LM scores between groups ($p = 0.474$). After treatment, the mean LM score was 3.94 (SD ± 4.69) in the intervention group and 5.10 (SD ± 5.91) in the placebo-control group. There was a positive correlation between the LM and the SNOT-20 scores ($r = 0.37$; $p < 0.02$). Tables 4 and 5 show the extent of sinusitis 1 month after treatment.

Discussion

Sinusitis is a common disease, sometimes refractory to antimicrobial therapy and with a predilection for chronicity and recurrences. Formation of biofilms on the mucosa of sinuses is considered important in the pathogenesis of chronic sinusitis. It has been shown that antibiotics in usual doses are ineffective in the eradica-

Table 3. Sinus involvement in the placebo group before treatment (n = 21)

Sinus	None n (%)	Mild n (%)	Moderate n (%)	Marked n (%)	Complete n (%)
Right fronta	10 (47.6	7 (33.3)	2 (9.5)	2 (9.5)	0
Left frontal	16 (76.2)	0	5 (23.8)	0	0
Right maxillary	5 (23.8)	2 (9.5)	7 (33.3)	4 (19.0)	3 (14.3)
Left maxillary	8 (38.1)	0	5 (23.8)	8 (38.1)	0
Right anterior ethmoidal	11 (52.4)	2 (9.5)	1 (4.8)	4 (19.0)	3 (14.3)
Left anterior ethmoidal	9 (42.9)	3 (14.3)	2 (9.5)	4 (19.0)	3 (14.3)
Right posterior ethmoidal	12 (57.1)	0	4 (19.0)	3 (14.3)	2 (9.5)
Left posterior ethmoidal	12 (57.1)	2 (9.5)	3 (14.3)	2 (9.5)	2 (9.5)
Right sphenoidal	19 (90.5)	2 (9.5)	0	0	0
Left sphenoidal	0	0	0	0	0

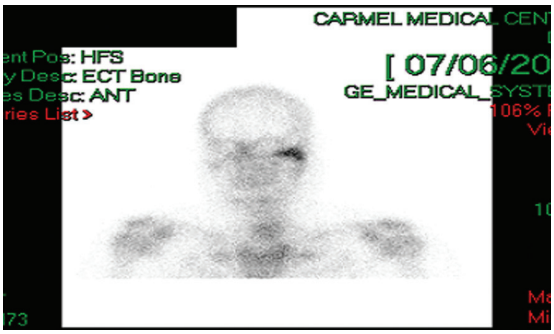

Figure 2. At initial presentation, patient 2 has a positive bone scan.

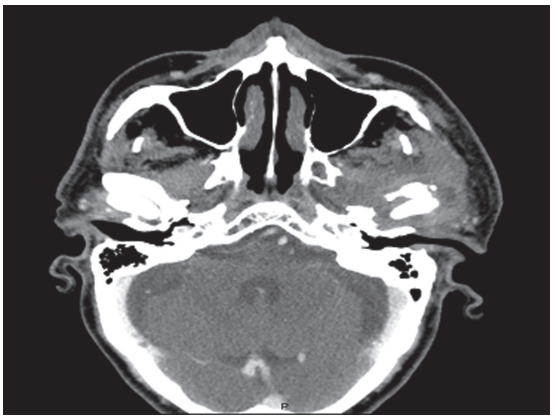

Figure 3. A CT scan with contrast from patient 2 demonstrates hypertrophy of the external ear canal, involvement of the infratemporal fossa, and a small collection of pus lateral to the temporomandibular joint.

and correlated findings on the initial CT scan to the severity of the clinical course.[12] They suggested that aggressive treatment should be initiated and that surgery might be needed when a patient presents with bony destruction involving at least two of the following areas: temporal bone, skull base, or temporomandibular joint.

We believe that the initial CT scan might be misleading in certain cases, such as when the disease is of fungal etiology. In those cases, although the patient may present with an initial indolent CT scan, the disease will worsen if proper antifungal therapy is not administered. Isolating a fungal pathogen from the surgical tissues was possible in 4 of 5 patients. This observation suggests that a fungal etiology is likely when NOE is refractory to the regular systemic antibacterial therapy.

We usually judge refractoriness of disease according to its clinical course. Surgical intervention is contemplated when no improvement occurs after 3 weeks of in-hospital treatment (preferably a culture-based regimen).

Before surgery, we prefer to obtain a new CT scan to evaluate the extent of the disease and plan the surgical approach. In those refractory NOE cases, the aim of surgery is to obtain deep biopsy, cultures, and PCR samples. Other suggested relative indications for surgical interventions for NOE are summarized in table 3.

Systemic therapy is, of course, still necessary after surgery, yet after receiving the results of cultures and PCR, we can better tailor the antibacterial or antifungal medications to promote healing. We take samples for PCR in case the cultures are not informative in isolating a pathogen. Obtaining samples for PCR, however, is not necessary routinely; nevertheless, we believe it may be beneficial in these severe cases and when the samples are taken under sterile conditions during surgery. There is no literature to support the use of this laboratory test and no information regarding its sensitivity and specificity under these circumstances.

Another option is hyperbaric oxygen therapy (HBOT), which has been described as having the potential to improve healing in NOE patients.[13] A Cochrane review concluded that no clear evidence exists to support HBOT as an effective modality for the treatment of NOE.[14] That conclusion is based on the absence of published

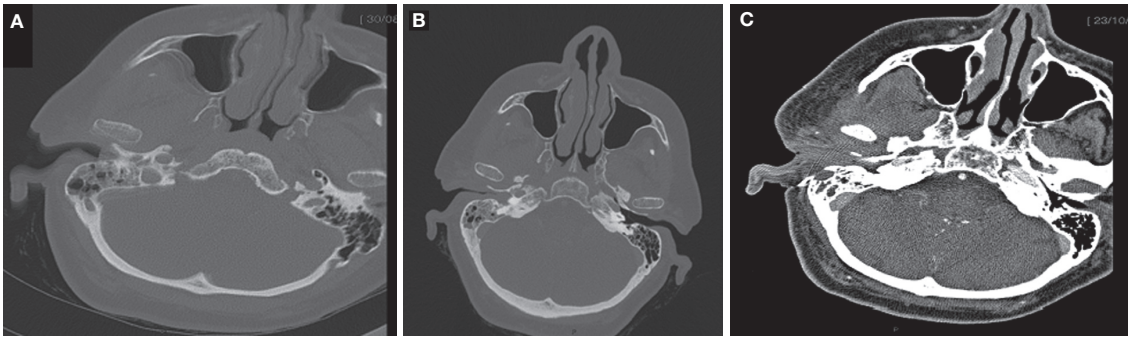

*Figure 4. CT scans from patient 3 show external canal swelling and middle ear and mastoid opacification (**A**), propagation of the infectious process (**B**), and further deterioration: external canal swelling, middle ear and mastoid opacification, erosion of the mandibular condyle, infratemporal fossa involvement, and parapharyngel space involvement (**C**).*

Table 3. Suggested relative indications for surgical intervention in NOE

Refractory necrotizing otitis externa, as determined by biopsy, cultures, and PCR
Abscess drainage
Treatment of complications (nerve decompression, etc.)
Facilitating drainage pathways
Rule out malignancy

randomized, controlled studies of the efficacy of HBOT, although noncontrolled studies did suggest HBOT to be of benefit.[15] In these studies, HBOT augmented medical therapy in severe cases and proved effective. HBOT is an attractive alternative, especially when managing high-risk surgical candidates, and it is already an accepted treatment modality in some institutions. Combining surgery with HBOT may be an option in severe cases, although no studies have addressed this issue.

To conclude, NOE is a severe otologic infection with potentially devastating consequences. Systemic and topical treatments are the mainstay in most cases, yet a subset of patients may benefit from surgical intervention.

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