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Efficacy of a nasal spray containing N-acetylcysteine in hypertonic saline solution in the treatment of chronic rhinosinusitis, with early recurrence after Functional Endoscopic Sinus Surgery

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Abstract

A retrospective clinical study was conducted to evaluate the efficacy of a nasal spray containing N-acetylcysteine (NAC) in hypertonic saline solution in improving symptoms in subjects with an early recurrence of chronic rhinosinusitis (CRS) after Functional Endoscopic Sinus Surgery (FESS). Twenty patients (14 males, 6 females, mean age 52.6 years) suffering from bilateral CRS who had already undergone FESS 1 to 4 times were evaluated. The clinical study consisted of two phases: the first lasted 6 months (from T0 to T1). Patients received only the standard drug therapy; the second phase lasted 3 months (T2 after one month of therapy, T3 after 3 months of nasal spray therapy) and was characterized by the combination of nasal spray with the standard therapy. At the beginning of the study and at each follow up visit, patients completed a generic visual analog scale (VAS) and a specific VAS and underwent nasal endoscopy. From T0 to T1, i.e. following standard therapy alone, patients did not show any significant changes versus baseline in the scores reported on the generic (P = 0.145) and specific VAS scales (P = 0.106). From T1 to T2, i.e. after combining the nasal spray with the standard therapy for one month, a statistically significant improvement was observed on both the generic and specific Vas scales.

On average, generic VAS scores decreased by about 2.2 and 2.6 points after 1 (T2) and 3 months (T3) from the start of nasal spray therapy ($P < 0.0001$). In addition, the mean values of the specific VAS showed a statistically significant decrease by about 2.9 and 3.4 points after 1 (T2) and 3 months (T3) from the start of nasal spray therapy ($P < 0.0001$).
The endoscopic examination showed that mucus had disappeared or significantly improved after the first month of nasal spray therapy ($P < 0.001$). During the observation period, no patient reported adverse effects that could be related to the nasal spray and no patient discontinued this treatment. The evidence gathered suggests that the combination of standard therapy and a nasal spray containing hypertonic saline solution and NAC in patients with CRS and an early recurrence after FESS, may be beneficial.

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease of the nasal mucosa and sinuses accompanied by a stuffy nose, rhinorrhea, dizziness, headache and is characterized by alternating symptoms [1]. CRS is considered one of the most common chronic upper airway diseases in developed countries. There is evidence that both its prevalence and incidence are on the rise. Estimates show a global prevalence varying between 1.0% and 12.1% [2]. It adversely affects the quality of life of patients and their ability to work and has a considerable impact on the healthcare expenditure [3,4].
CRS often develops together with nasal polyposis and bronchial asthma [5]. The Samter's Triad (ST) is a form of CRS that typically combines nasal polyposis, asthma and intolerance to aspirin and NSAIDs. Thanks to the growing popularity of endoscopic sinus surgery (Functional Endoscopic Sinus Surgery - FESS), the success rate of this procedure has significantly increased [6]. However, the risk factors influencing the clinical prognosis of CRS patients remain unclear, as evidenced by the high recurrence incidence after surgical treatment [7].
The functional integrity of paranasal sinuses requires a continuous air exchange with the nasal cavities and a normal mucociliary clearance to release secretions. In case of insufficient mucociliary transport, secretions stagnate, promoting the establishment of pathogenic germs and chronic inflammation. Three different pathogenetic aspects have been identified in the onset of CRS: obstructed communication ostia, defective mucociliary transport, qualitative and quantitative mucus alterations. These three pathogenetic conditions do not act in isolation, but are part of a vicious circle that progressively fosters the chronic rhinosinusitis process [8].
The authors of the present clinical study work at a combined otolaryngology outpatient clinic of the Otolaryngology Department of the Manerbio Hospital (Brescia, Italy). They see CRS patients with an early recurrence of polyposis and rhinosinusitis infection after FESS, despite a standard post-operative therapy.
Patients are examined from an allergological, immunological and pneumological point of view. Allergology and otorhinolaryngology specialists jointly examine and plan a personalized therapy.

Aim of the study

CRS patients with nasal polyposis and ST are ideal candidates for FESS surgical treatment to preserve their physiological structures and mucociliary drainage. However, functional surgery may not solve the problem and is characterized by frequent recurrences. Hence, medical therapy with drugs to control inflammation and symptoms and to treat asthma comes into play. Sometimes, therapy is initiated to desensitize to acetylsalicylic acid, which may allow an improvement in rhinosinusitis and asthma.
Nasal endoscopy often shows mucus in the nasal fossae or ostia of these patients. Mucus is thickened and viscous, so as to alter the ciliary activity of the opposing mucous surfaces. This leads to persistent pathogenic noxae and accumulation of mucus in the sinuses, promoting an edematous state of mucous membranes causing sinusitis. Patients complain about a clinical disorder characterized by persistent mucus with an annoying rhinopharyngeal discharge. In order to mechanically remove excess mucus, patients included in the study were encouraged to apply the nasal spray under investigation, consisting of a hypertonic saline solution containing N-acetylcysteine (NAC), during the day.
The main objective of this clinical study was to confirm that a combination of nasal spray containing NAC in hypertonic solution and the standard therapy may represent a therapeutic option to improve symptoms and clinical prognosis while reducing the risk of recurrence after endoscopic sinus surgery.
The primary outcome of the present clinical study is the evaluation of the efficacy of Viscoflu® Nasal Spray in patients with CRS and ST, by periodically repeating the endoscopic nasal examination and by filling in visual analog scales. The secondary outcome is the evaluation of the safety of use of the nasal spray.

Materials and methods

Population

Twenty patients were evaluated (14 males, 6 females, mean age 52.6 years, minimum age 17, maximum age 77 years). They suffered from CRS bilateral and had a history of 1 to 4 FESS procedures. CRS was diagnosed through their history, objective examination, nasal endoscopy and allergic tests.
Skin prick tests were carried out in accordance with the validated criteria [9]. Allergy was detected in 6 patients (30%); 5 patients were polysensitized (25%), 14 patients had asthma (70%), 2 patients suffered from gastroesophageal reflux, 4 patients from hypertension, 7 patients from aspirin intolerance (acetylsalicylic acid, 35%), 6 patients had aspirin sensitivity associated with asthma (30%). Clinical data about the study patients are reported in Table I.

Table I. *Clinical data of study patients. Data reported in the table show that the two groups of patients, affected and unaffected from ST, do not have any significant differences with respect to the prevalence of these parameters.*

Variable	All patients (n=20)	ST patients (n=7)	Non-ST patients (n=13)	P-value
Age (years), mean ± DS (min age – max age)	53 ± 17 (17 – 77)	53 ± 17 (28 – 70)	52 ± 18 (17 – 71)	0.888
Comorbidities (GERD, hypertension), % (n)	30 (6)	29 (2)	31 (4)	1.000
Asthma, % (n)	74 (14/19)	86 (6)	67 (8/12)	0.603
Allergies, % (n)	30 (6)	43 (3)	23 (3)	0.613
Previous procedures ≥ 2, % (n)	45 (9)	57 (4)	38 (5)	0.642

Medical device employed in the study

Viscoflu® Nasal Spray (Pharma Line, Milan, on the market since July 2018) is a medical device containing 3% hypertonic saline solution (NaCl), with controlled pH, and 6% NAC. The product is indicated to facilitate the fluidification and removal of mucous or mucopurulent secretions stagnating

in the nasal cavities and paranasal sinuses. It is indicated to improve the symptoms and course of acute, subacute and chronic inflammation of the upper airways.
NAC has a mucolytic action. It can separate the disulfide bridges that characterize many mucoproteins, thanks to the free thiol group interacting with the bonds responsible for the aggregation of mucoproteins and therefore the high viscosity of mucus. By breaking the bonds, mucoproteins are split into less viscous, smaller units. NAC stimulates glutathione biosynthesis, promotes detoxification and is directly involved in neutralizing free radicals. It therefore has an antioxidant activity and counteracts the generation of reactive oxygen species [10,11].
Studies have shown that NAC exhibits anti-inflammatory properties by inhibiting NF-kB nuclear factor and modulating the synthesis of pro-inflammatory cytokines [12,13]. Although NAC is not an antibiotic, it has antimicrobial properties and counteracts the formation of bacterial biofilms [14]. The hypertonic solution, exploiting the osmotic gradient, promotes the retrieval of water from the cells and therefore reduces submucous oedema. It also improves the mucociliary clearance by stimulating mechanical cleansing. This reduces symptoms in patients with upper airway disease [15,16].

Study design

This is a retrospective clinical study.
The clinical study consisted of two phases: in the first phase, patients received only the standard therapy; the second phase was characterized by the combination of Viscoflu® Nasal Spray with standard therapy. The clinical study process is summarized in Table II.

Table II. *Phases of the clinical study.*

FIRST PHASE OF THE STUDY		SECOND PHASE OF THE STUDY		
T0	T1		T2	T3
Initiation of standard therapy after FESS	Check-up after 6 months from the initiation of standard therapy	Start of therapy with Viscoflu® Nasal Spray in combination with standard therapy	Follow-up visit at 1 month from T1, after a course of therapy with Viscoflu® Nasal Spray	Follow-up visit at 3 months from T1, after 3 cycles of therapy with Viscoflu® Nasal Spray

First phase of the study

The first phase of the study (from T0 to T1) lasted 6 months. It was characterized by a personalized medical treatment, based on the clinical staging and symptoms and cycles of drug administration reported in Table III representing the therapy of the first phase of the study, which represent the standard therapy.

Second phase of the study

The second phase of the study (T1 to T2 to T3) lasted 3 months. Patients continued with their previous therapies, except for one patient who stopped standard therapy.
From T1 to T3, patients continuously combined the standard therapy with Viscoflu® Nasal Spray (2 sprays per nostril 3 times a day, for 10 consecutive days a month, for 3 consecutive months).
At all visits (from T0 to T3), nasal endoscopy with 0 or 30° rigid optics was repeated, including a visual evaluation of the mucus. Patients completed, during all visits, a generic visual analog scale (generic VAS) in which they had to answer the question: in the last month, how annoying were your nasal symptoms? The scale ranged from 0 to 10, where 0 means no symptoms and 10 means the greatest discomfort ever experienced. Patients also completed a specific visual analog scale (specific VAS) during all visits to answer the question: How annoying were the following symptoms: nasal obstruction, facial pain, loss of sense of smell, pharyngeal mucous discharge, rhinorrhea, nasal itching, sneezing, itchy eyes, watery eyes, coughing, chest tightness, shortness of breath, dyspnea in the last month? The scale ranged from 0 to 10, where 0 means no symptoms and 10 means the greatest discomfort ever experienced. Finally, at all visits, patients were asked to report any disorder they had suffered in the period between visits to assess the therapy safety and tolerability.

A standard therapeutic approach based on clinical staging and symptoms was followed with all patients, who regularly took the therapy assigned to them both in the first and second phase of the study.

Table III. *Pharmacological therapies in the first phase of the study. In the second phase, all subjects continued the pharmacological therapy of the first phase, except for a ST patient who discontinued the therapy. In the first phase, this subject had received inhaled corticosteroid + beta 2 agonist and corticosteroid spray.*

Trattamento*	All patients (n=20)	ST patients (n=7)	Non-ST patients (n=13)	P-value
No treatment, % (n)	15 (3)	14 (1)	15 (2)	1.000
Inhaled corticosteroid + beta 2 agonist, % (n)	40 (8)	57 (4)	31 (4)	0.356
Anti-leukotriene, % (n)	20 (4)	43 (3)	8 (1)	0.101
Corticosteroid per os, % (n)	50 (10)	43 (3)	54 (7)	1.000
Other, % (n)	25 (5)	57 (4)	8 (1)	0.031

(*) 15% (n = 3) of patients did not receive any drug therapy, 50% (n = 10) received 1 treatment (9 non-ST, 1 ST patient), 35% (n = 7) received two or more treatments (2 non-ST, 5 ST patients). Other: inhaled bronchodilator, corticosteroid spray, per os antihistamine, statin, anti-IL5, ASA desensitization.

Statistical analysis

The main purpose of the statistical analysis was to evaluate the efficacy of Viscoflu® Nasal Spray, in combination with the standard protocol for the treatment of CRS patients with an early recurrence after FESS, compared to the standard drug therapy alone. Data obtained after 6 months of standard therapy were then compared with data obtained after 1 and 3 months of therapy with Viscoflu® Nasal Spray combined with standard therapy.
The age t-test was used for table I with demographic and clinical data; the exact Fisher test was applied for categorical data. The exact Fisher test was also applied for Table III with standard drug therapies. As to the longitudinal analysis, a mixed linear model was applied, with only a random intercept while the time variable was entered as a categorical one. As regards the qualitative and quantitative evaluation of mucus, the Stewart-Maxwell test was employed. The R version 3.6.1 software for Windows (R Core Team; 2013. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) was employed for statistical processing.

Results

The mean scores of patients on the generic and specific VAS scales are shown in Table IV.

Table IV. *Mean scores reported by patients on the generic and specific VAS scales during the clinical study.*

	T0	T1	T2	T3
Generic VAS Mean (95% CI) (*)	5.3 (4.7 – 6.0)	5.9 (4.5 – 7.2)	3.7 (2.3 – 5.0)	3.3 (1.9 – 4.6)
Specific VAS Mean (95% CI) (*)	5.9 (5.1 – 6.7)	6.7 (5.0 – 8.4)	3.8 (2.1 – 5.5)	3,3 (1.6 – 4.9)

(*) values were estimated using a mixed linear model).

From T0 to T1, i.e. after 6 months of standard therapy, patients did not show significant changes from the initial scores reported on the generic VAS scale (P = 0.145; figure 1) and on the specific VAS scale (P = 0.106; figure 2). From T1 to T2, i.e. after combining Nasal Viscoflu® Spray with the standard therapy for one month, a statistically significant improvement was observed, considering the average scores reported both on the generic and specific Vas scale. In fact, on average the generic VAS scores decreased in a statistically significant manner by about 2.2 and 2.6 points after 1 (T2) and 3 months (T3) from the beginning of therapy with Nasal Viscoflu® Spray (P < 0.0001; figure 1). In addition, the mean scores of the specific VAS decreased in a statistically significant manner by approximately 2.9 and 3.4 points after 1 (T2) and 3 months (T3) of Nasal Viscoflu® Spray therapy (P < 0.0001; figure 2). There are no differences in the response pattern between subjects affected or unaffected by ST either for the generic (P = 0.248) or specific VAS (P = 0.395).

Figure 1. *Change in mean score on the generic VAS scale over the observation period (T0 = start of observation of patients treated with standard drug therapy, T1 = follow-up visit after 6 months of standard therapy and start of therapy with Viscoflu® Nasal Spray; T2 = follow-up visit after 1 month of therapy with Viscoflu® Nasal Spray; T3 = follow-up visit after 3 months of therapy with Viscoflu® Nasal Spray *** = P < 0. 0001).*

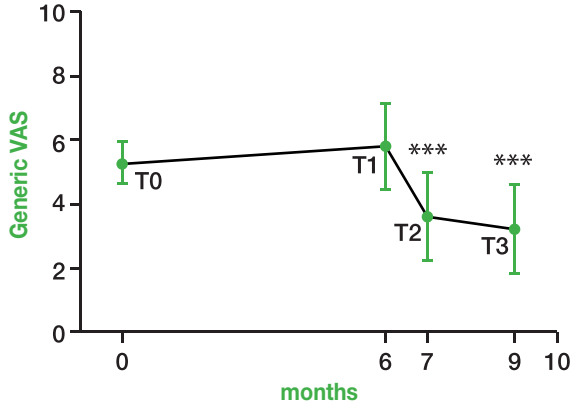
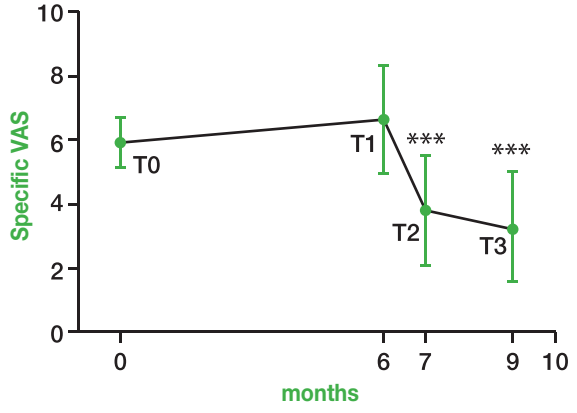


Figure 2. *Change in mean score on the specific VAS scale over the observation period (T0 = start of observation of patients treated with standard drug therapy, T1 = follow-up visit after 6 months of standard therapy and start of therapy with Viscoflu® Nasal Spray; T2 = follow-up visit after one month of therapy with Viscoflu® Nasal Spray; T3 = follow-up visit after 3 months of therapy with Viscoflu® Nasal Spray; *** = P < 0.0001).*



Endoscopy showed that mucus had disappeared or significantly improved after the first month of treatment with Viscoflu® Nasal Spray. This data is statistically significant (P < 0.001; figure 3).

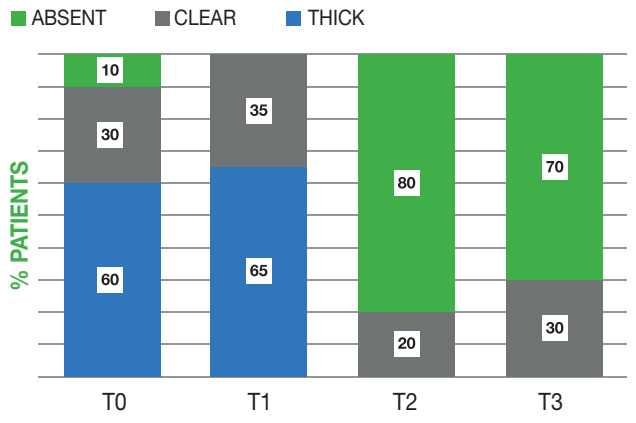
During the observation period, no patient reported adverse effects related with the use of Viscoflu® Nasal Spray and no patient discontinued this treatment.

Discussion

CRS patients experience significant differences in terms of clinical symptoms, disease severity and prognosis. Today, FESS has become a well-established strategy for the treatment of drug refractory CRS. However, due to the complex and unclear influence of various factors, it is still difficult to

predict the clinical prognosis of CRS patients undergoing FESS. The use of standard post-FESS drug therapy does not always allow a satisfactory therapeutic outcome. Therefore, the objective of this study is to provide data about FESS patients with an early recurrence, suggesting the addition of a second therapy to the standard drug therapy.
In this retrospective clinical study, the application of a nasal spray containing NAC and hypertonic saline solution for 10 consecutive days a month, for 3 consecutive months, was associated with the improvement of perceived symptoms in CRS patients who had already undergone FESS. More specifically, the mean score of generic and specific VAS scales decreased and the investigators observed the disappearance of mucus or the improvement of its quality.
Viscolfu Nasal Spray was very well tolerated, as proven by the absence of adverse event reports.
These promising results are especially interesting and relevant when considered in the context of CRS with an early recurrence after FESS, a condition characterized by a still unmet medical need, despite its prevalence and its associated deterioration in the quality of life. Of great interest is also the high tolerability and appreciation shown by patients for the therapeutic solution proposed in this paper.
A limitation of the present study could be the lack of a control arm. However, it should be noted that patients first received the standard drug therapy and, given their not fully satisfactory results, subsequently applied the nasal spray in addition to the standard therapy, which they continued. This procedure has allowed obtaining comparative data that, in spite of the small sample size, can be used as a basis for further clinical studies. On the other hand, the benefits of NAC and hypertonic solution on respiratory mucous membranes have been clearly highlighted in the literature [10-18].

Figure 3. *Results of mucus evaluation during endoscopic examination (6 months of standard therapy versus 1 month of standard therapy in combination with Viscoflu® Nasal Spray: chi-squared = 17.333, df = 2, P < 0.001).*



Conclusions

A CRS patient after FESS surgery requires regular follow up visits to check the surgical outcome and inflammation of the nasal mucosa. This is needed to set up an appropriate post-operative medical therapy. Post-surgical management provides for the use of any drugs required for a personalized therapy (precision medicine) [19]. In view of the frequent endoscopic findings of dense and persistent mucus, it was decided to introduce, in addition to the standard therapies, Viscoflu® Nasal Spray at the dose indicated in the package leaflet (2 deliveries per nostril 3 times a day, for 10 consecutive days). After verifying the efficacy of this therapy, it was decided to repeat cycles for at least 3 consecutive months. The results of this clinical study demonstrate the efficacy and safety of the combination of the medical device Viscoflu® Nasal Spray with the standard therapy to improve symptoms, reduce the amount of mucus and improve its characteristics and prevent the onset of nasal polyps in patients with CRS and ST with an early recurrence after FESS.
Viscoflu® Nasal Spray has been shown to be safe and well tolerated; no patient has reported any adverse effects and no patient discontinued this therapy.
Despite the limited clinical data available, the evidence gathered suggests that the combination of a 3% hypertonic saline and 6% NAC nasal spray with standard therapy is potentially beneficial in patients with CRS and ST who have had an early recurrence after FESS surgery.

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