

A randomized single-blind study to evaluate antiinflammatory effectiveness of Erbal nasal spray.

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Abstract

The nose is the gateway for the airways and this important function is related to air macrofiltration and its moisturization, performed by the nasal mucosa.

Dust, air pollutants, pollen, bacteria, and viruses are first picked-up by the nasal mucus and then moved posteriorly by the ciliary-cell clearance system of the respiratory epithelial cells. Both the mucus and the cilia prevent the progression of foreign substances, such as dust and pollutant particles, which otherwise could enter the respiratory tract along with inhaled air. The postoperative mucosal damage due to surgery performed for chronic rhinosinusitis has always been a challenge, in the immediate follow-up the patient needs to be specifically treated with the purpose of restoring the normal function of the nasal mucosa as soon as possible. The use of a combination of various natural products has demonstrated to be able to deal with nasal inflammation. In fact it was shown that Erbal Nasal Spray nasal spray can improve nasal breathing, enhance mucosal oedema, but above all it showed to improve mucosal cellular function and nasal cellularity.

INTRODUCTION

The nose is the gateway to the airways and its mucosa represent the first line defence: the ciliated respiratory epithelial

cells are responsible for the ciliary clearance system that moves posteriorly the nasal mucus, preventing the progression of foreign substances like

dust, pollutants, pollen, bacteria and viruses.

Conditions that affect the nasal clearance system and the nasal mucosa such as allergies and nasal dryness may be dangerous and need to be adequately treated in order to avoid chronicization of the inflammatory process, that could possibly extend to lower airways.

The use of natural products could represent an alternative to topical steroids and anti-histamines in the treatment of nasal mucosa chronic inflammatory diseases. We are therefore presenting a study conducted with the aim to assess anti-inflammatory performance and safety of Erbal nasal spray in comparison to placebo.

DESIGN OF THE STUDY

Objective

Primary endpoint of this study was to assess effectiveness on nasal mucosa health determined by the Lund-Kennedy score (**Figure 1**) and feasibility of Erbal nasal spray (a composition of Calendula Officinalis L., Alnusglutinosa Gaerth, Ribes Nigrum L., Abies Pectinata D.C., Rosa Canina L., Perilla Frutescens L., Manganese Gluconate) in comparison to placebo. Secondary endpoints were to determine variations into quality of life by analysing a Snot-22 questionnaire (**Figure 2**) and to evaluate changes in nasal

secretions' composition by nasal cytology examination. Particular attention was paid also to eventual adverse events given by the drug and possible changes in vital functions' values during and after the treatment period.

Patient enrollment

Recruiting period was 12 weeks. Patients of both sex, aged between 18 and 70 years old, affected by chronic rhinosinusitis without polyposis were selected for the study.

Inclusion Criteria were the followings:

- Capability to understand and take informed consent
- Ability to follow the instructions
- Ability to undergo the scheduled monitoring visit

Exclusion criteria were the followings:

- Women who were pregnant or breastfeeding
- Deviation of the nasal septum
- Bleeding or recurrent epistaxis
- Use of systemic antibiotics in the last 30 days
- Known hypersensitivity to any component of the preparation to be administered
- Concurrent topical application of other drugs at the nasal level
- Patients participating in any other pharmacological study

METHODS AND STUDY POPULATION

The study was randomized, single-blinded, divided into two groups and conducted into 4 Otorhinolaryngologic departments; in the following hospital: ENT Massa Carrara, ENT Codogno, Ent Clinic Federico II Napoli and the ENT Clinic University of Insubria, A.S.S.T Sette Laghi, Varese.

The duration of the study was 12 months; 12 weeks were dedicated to the enrolment of the patients; while the effective treatment period was 24 weeks.

At the first visit (V0) all patients' data were collected (demographic information, past and recent medical history, pharmacological history and vital parameters), the quality of life was determined according to Snot-22 questionnaire, an endonasal endoscopic clinical evaluation was performed using a rigid 0° angled endoscope, and also the microscopic examination of the nasal mucosal cells was performed.

Eligible patients were randomized in 1: 1 ratio to one of the 2 treatment groups, namely:

Group 1): patients treated with Erbal nasal spray (composition: Calendula officinalis, Alnusglutinosa, Ribes nigrum, Abies pectinata, Rosacarin, Perilla frutescens, gluconate manganese).

Group 2): control group, patients treated with placebo (solution of isotonic sea

water).

Patients performed 3 nebulization each nostril, 3 times a day at 6-hour intervals each, for 30 consecutive days; followed by 30 days of interruption period and subsequent new treatment cycles equal to the previous, for 3 treatments total.

At the end of the first cycle of treatment (12 weeks) patients returned to the referring centre to undergo the first control visit (V1) where another SNOTT-22 questionnaire on the quality of life was filled-in and where vital functions and eventual adverse events were collected.

After 24 weeks (V2), patients underwent the final examination: another snot-22 questionnaire was filled-in, a new endonasal endoscopy evaluation and a new cytological examination on nasal mucosa were performed.

The 4 centres enrolled 172 patients; 51 later jumped-off the study because of lack of compliance while taking the therapy and/or fault in joining the prescribed follow-up. The statistics analysis were therefore calculated on 121 patients: 10 patients from the centre in Massa Carrara, 10 patients from Cremona, 40 patients from Napoli and 61 from Varese.

The gender prevalence was: 61 females and 70 males with a mean age of 52,6 years (18-71).

The two groups of the population were composed as follows: **Group 1** included

60 patients (32 M and 28 F) and **Group 2** including 61 patients (30 M and 31 F).

Methods:

The endonasal endoscopy was performed using a Karl Storz rigid endoscope 0° angled, paying particular attention to the presence of anterior discharge, mucosal oedema, mucosal tropism, and inferior turbinates' swelling. To each patient a Lund-Kennedy Endo-score was assigned(1). Rhinorrhea was considered to be absent (0), mild (1) or severe (2). Mucosal oedema and reddening were as well considered to be absent (0), mild (1) or severe (2). The status of nasal mucosa was classified as eutrophic (1), hyperemic (2) or dystrophic (3). Inferior turbinates were considered to be normal (0), slightly hypertrophic (1), hypertrophic (2) or severely hypertrophic (3).

Snot-22 questionnaire was filled-in before, during and after the treatment and it was used to determine the presence and severity of symptoms and patient's quality of life.

Nasal cytology was performed before and after the treatment. The diagnosis of nasal disorders through nasal cytology is based on the consideration that in healthy subjects, the nasal mucosa is made of 4 normal subsets of cells; besides neutrophils, no other cells are normally detected in healthy individuals. Therefore

the presence of eosinophils, mast cells, bacteria and fungi must be considered as sure sign of nasal pathology (2).

RESULT

The primary endpoint was to assess the nasal mucosa health by the Lund-Kennedy Endo-score. At the end of the study a difference between both groups was noticed in terms of improvement for 30% patients in the group treated with placebo and 35% improvement for patients treated with Erbal Nasal Spray.

The primary end point represented by the nasal evaluation using the Lund-Kennedy score modified to observe a difference between the two treatments by 30% with a superiority of the placebo-treated water treatment was achieved with a value of 35%.

In particular the nasal endoscopy showed a statistically significant increase of the analysed values, except from rhinorrhea (**Tables 1-2-3-4**).

As a secondary endpoint Snot-22 questionnaires on quality of life were analysed. Group 2 showed a significantly increase in quality of life in comparison to Group 1 (**Table 5**).

Also the nasal cytology examination, performed before and after the treatment, showed a significantly improvement in the group that used Allerdep (**Table 6**).

No adverse events and no changes in vital signs were noticed during the study.

Rhinorrea	V0		V1		V2		p-value
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
Absent	20	25	30	26	38	26	n.s.s.
Low	30	25	25	24	18	25	
Hight	10	11	5	11	4	10	

Table 1. Endoscopic endonasal evaluation of nasal secretions. The comparison between the two groups showed an improvement of the rhinorrea in Group 2, even if the data were not statistically relevant.

Oedema	V0		V1		V2		p-value
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
Normal	29	30	38	30	45	35	0,079
Low	30	30	21	30	15	23	
Heavy	1	1	1	11	0	3	

Table 2. Endoscopic endonasal evaluation of nasal mucosa oedema. The mucosal oedema appeared to be decreased in the group treated with Erbal Nasal Spray but the analysis showed to be not statistically significant.

Nasal Mucosa	V0		V1		V2		p-value
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
Eutrophics	20	15	29	20	48	30	0,0031
Iperemic	1	2	1	1	0	1	
Distrofic	39	44	30	40	12	30	

Table 3 Action of Erbal Nasal Spray on mucosal trophism. The efficacy of Erbal Nasal Spray on mucosal trophism was noticed and the statistics analysis was significant ($p < 0,05$).

Turbinates	V0		V1		V2		p-value
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
Normal	20	25	30	28	48	30	0,0006
Low	20	20	15	22	12	25	
Media	20	15	15	10	0	6	
High	0	1	0	0	0	0	

Table 4. Effects on inferior turbinate's hypertrophy. It was seen a significant improvement in Group 2 in comparison to Group 1 with a p value $< 0,05$.

SNOT-22	V0		V2		p-value
	Group 1	Group 2	Group 1	Group 2	
Medium values	16	15	5	10	0,0056

Table 5. Analysis of SNOT-22 questionnaire. It shows a significant increase in quality of life in patients treated with Erbal Nasal Spray.

Nasal Citology	V0		V2		p-value
	Group 1	Group2	Group 1	Group2	
Eosinophils	25%	34%	12%	29%	0,0002
Mastcells	39%	41%	10%	22%	0,003
Bacteria	1 %	2%	0%	0%	n.s.
Micetis	0 %	0%	0%	1%	n.s.
Siss	30 %	41%	79%	50%	0,0001
Linfocitis	3 %	2%	2%	2%	n.s.

Table 6. Microscopic examination of the nasal mucosa (nasal cytology): *Erbal Nasal Spray showed to have a positive effect reducing the inflammatory cells in comparison to the group who received placebo. In particular it was noticed and improvement of the cellular vitality by an increase of the supranuclear stria (Siss $p=0,0001$).*

DISCUSSION

The nose is the gateway for the airways and this important function is related to air macrofiltration and its moisturization, performed by the nasal mucosa.

Dust, air pollutants, pollen, bacteria, and viruses are first picked-up by the nasal mucus and then moved posteriorly by the ciliary-cell clearance system of the respiratory epithelial cells. Both the mucus and the cilia prevent the progression of foreign substances, such as dust and pollutant particles, which otherwise could enter the respiratory tract along with inhaled air.

The activity of the nose work best at about 50% humidity, if moisture is less than this value, mucus clearance is slowed down and ineffective, leading to a vicious circle of secretion stagnation and increased risk of inflammation.

The mucus contains on average 95% of water. Endonasal anatomy seems to favor a turbulent intake of inhaled air and improves the deposition of airborne particles on the mucus layer. The cilia located at the apical pole of the epithelial cells are only functional when surrounded by mucus layer. The ciliary beats have a

frequency of 10-15 Hz and allow the mucus layer to be transported to the back of the nasal droplets at a speed of 10-15 mm/min. Small variations in the composition mucus can modify the mucociliary function significantly. In case of modification of the amount and/or the quality of the mucus, an increase in bacterial adhesion to the epithelial surface is observed and this mechanism could play an important role in the development of chronic rhinosinusitis.

Nasal dryness is also due to chronic pathological conditions (such as sinusitis and allergic rhinitis) or persistence in dry, dusty and polluted environments, frequent frictional sneezing, frequent nose bleeding, crusts in the nasal cavity or contact with allergens, irritants, smoke, smog or microorganisms.

The importance of adequately treating the pathologies that may affect nasal cavities such as nasal dryness is important to prevent chronicization of the inflammatory processes typical of rhinosinusitis and to prevent asthma and other inflammatory pathologies of the lower airways . Rhinosinusitis can be classified as acute or chronic. Acute Rhinosinusitis (ARS)

lasts less than 12 weeks with complete symptoms' resolution.

Rhinosinusitis is a multifactorial pathological process. Chronic inflammation of the nasal cavity may lead to obstruction of drainage in this area. This leads to poor ventilation and drainage of the paranasal sinuses causing their inflammation and infection. Inflammation and subsequent bacterial infection of paranasal sinuses may occur after a common viral infection, after allergic and non-allergic rhinitis and after ciliary system disorders (as seen in cystic fibrosis and Kartagener's syndrome). Anatomic abnormalities of the middle turbinate or ethmoidal sinuses may block the ventilation of sinus especially if there is an additional inflammatory condition.

Some predisposing factors or co-morbidities are associated with chronic rhinosinusitis, and during the history collection of the patients the clinician should be informed on the following conditions: Smoking (also passive smoking, especially in children); Asthma - Up to 50% of patients with asthma suffer from CRS; Bronchial hyperactivity; Aspirin sensitivity (10% of asthmatic patients have asthma-induced asthma, triad sensitivity to aspirin, asthma and nasal polyposis is known as Samter's triad); Concomitant allergic rhinitis; Immune deficiency

syndrome; Hormone factors (hypothyroidism, or menopause).

Treatment of sinonasal pathologies arises from the synergy between medical and surgical therapy when needed, surgical therapy is a means of correcting the presence of any anatomical alterations that do not allow the proper functioning of medical therapy, which remains the first choice in treatment. During the first 6-9 months after surgery it is advisable to prefer topical steroid therapy; lately it could be suspended and it is possible to consider other treatments.

The anti-allergic effects of a combination of phytoterapeutics is already object of studies (4) but the current one has the purpose of investigating also anti-inflammatory action of natural remedies on patients affected by chronic rhinosinusitis without poliposys. Phytomedicine could become an alternative treatment to topical steroids and anti-histamines in case of chronic rhinosinusitis.

Blackcurrant (*Ribes nigrum* L.) represent a common medical plant used for allergic rhinitis, joint and muscles pain and seasonal illness (sore throat and upper airways diseases) due to its well-known anti-inflammatory and analgesic effects as it inhibits histamine and

prostaglandins synthesis and release. It also has anti-fungal and antioxidants effects thanks to polyphenols, vitamins and sacurentina which also have positive effects on circulation (5). Marigold (*Calendula Officinalis* L.) has anti-inflammatory, anti-fungal, antioxidants and anti-bacteria effects as it contains flavonoids, essential oils and triterpene alcohols. This herb is also used as immunomodulatory agent as it stimulates phagocytosis and collagen methabolysm (6). *Alnusglutinosa* (Black alder) seems to have anti-inflammatory, antipyretic and healing characteristics. White fir (*Abies pectinata* D.C.) is currently used in treatment of eyes and muscles diseases thanks to its content in vitamin A and trimetina. It also has antirheumatic and diuretic properties. Pink canine (*Rosa canina* L.) it is used against rhinitis, otitis and common cold. It is a major source of vitamin C. It has shown to be very useful in activating vitamin B9 that has anti-allergic effect. *Perilla* (*Perilla frutescens* L.) has anti-inflammatory and anti-allergic effects through changes in IgE synthesis and inhibition of lipoxygenase. Manganese performs antioxidant actions in bone maintenance and in the physiological formation of connective tissue so we can write that it has

antioxidant action helping tissue regeneration.

Erbal nasal spray is a combination of all such phytotherapeutics and its pharmacological effects are due to their synergic action.

A recent study conducted in 2016, even if conducted on a small number of patients, proved the anti-allergic action of Erbal Nasal Spray when compared to placebo (3); as it showed to suppress eosinophils and mast-cells infiltration in nasal tissues while significantly reduced mucosal oedema and nasal secretions.

CONCLUSIONS

The postoperative mucosal damage due to surgery performed for chronic rhinosinusitis has always been a challenge, in the immediate follow-up the patient needs to be specifically treated with the purpose of restoring the normal function of the nasal mucosa as soon as possible.

After a period of topical steroid treatment, the patient needs a continuous follow up and, above all, a time-sensitive treatment. The present study has shown how topical steroid, once the defined treatment cycle is over, can be replaced by natural therapy with products that can replay the anti-inflammatory effect of steroid therapy. The use of a combination of various natural

products has demonstrated to be able to deal with nasal inflammation. In fact it was shown that Erbal Nasal Spray nasal spray can improve nasal breathing, enhance mucosal oedema, but above all it showed to improve mucosal cellular function and nasal cellularity. The reduction of inflammatory cells was demonstrated by the cytologic examination on nasal mucus; and this indirectly demonstrates how nasal cytology represents a valid method for monitoring therapy's effectiveness.

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