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Efficacy and tolerability of bromelain in patients with chronic rhinosinusitis – a pilot study

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Abstract. *Efficacy and tolerability of bromelain in patients with chronic rhinosinusitis – a pilot study*. *Objectives*: To evaluate the efficacy, tolerability, and impact on quality of life (QoL) of bromelain tablets (500 FIP) in patients with chronic rhinosinusitis (CRS).
Methods: In this prospective, open-label observational pilot study, 12 patients suffering from CRS with (CRS+NP) or without (CRS-NP) nasal polyps who had undergone prior sinus surgery were treated with bromelain tablets (500 FIP) for three months. Efficacy was evaluated using symptom scores (Total Symptom Scores: TSS); a Total Rhinoscopy Score (TRS) was also determined. QoL was assessed by using the German, adapted version of the Sinonasal Outcome Test 20 (SNOT-20 GAV).
Results: Treatment with bromelain tablets (500 FIP) improved TSS, TRS and SNOT-20 GAV on average. This treatment was found to be more effective, however, for CRS-NP than for CRS+NP. The average intake was six tablets, equivalent to a daily dosage of 3000 FIP. No adverse events were observed.
Conclusion: Preliminary results indicate good tolerability, symptom control, and improvement in QoL for the treatment of CRS using bromelain tablets (500 FIP).

Introduction

Chronic rhinosinusitis (CRS) is a significant health problem with an overall prevalence of 10.9% in Europe, as diagnosed with the CRS diagnostic criteria stated in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS).[1] It is often associated with the substantial impairment of patients' quality of life (QoL).[2-4] CRS is sometimes even associated with lower QoL relative to other severe chronic diseases.[4]

EPOS 2012 defines CRS as an inflammation of the nasal and paranasal sinus mucosa.[3] It is characterised by the presence of two or more of four symptoms, one of which is either nasal obstruction/blockage/congestion or nasal discharge, with the other two symptoms being facial pain/pressure and/or reduction or loss of smell.[3] Furthermore, the clinical diagnosis must be based on specific endoscopic criteria and/or changes in CT findings.[3] Rhinosinusitis is regarded as chronic if the symptoms above persist for more than 12 weeks without complete resolution.[3] Nasal polyposis is considered a subgroup of CRS[3] and is one of the most frustrating diseases for clinicians because recurrence is the rule.[5] Consequently, it requires effective treatment that results in symptom relief and improved QoL. The wide range of choices for managing CRS includes topical or systemic corticosteroids, antibiotics, and saline irrigations.[6,7] Even with intensive medical treatment, not all patients achieve permanent symptom improvement.[3,7] It is therefore important to investigate alternative therapeutic approaches that can lead to an improvement in symptoms and QoL. It is preferable if these approaches are well accepted by patients and are therefore likely to produce good compliance.

Bromelain belongs to a group of proteolytic enzymes obtained from the stems and immature fruit of the pineapple plant (*Ananas comosus*).[8,9] Its anti-inflammatory and anti-oedematous effects mean that bromelain is an alternative to glucocorticoids.[9] In addition, its very low toxicity makes it suitable for treating chronic inflammatory diseases.[9]

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As early as the 1960s, symptom reduction and improvement in mucosal inflammation in rhinosinusitis patients were observed in double-blind, placebo-controlled studies looking at the conjunctive use of bromelain.[10,11] In these studies, however, the principle focus was on acute rhinosinusitis.

The present observational pilot study was conducted to observe the efficacy and tolerability of bromelain tablet (500 FIP) treatment and its impact on QoL in patients with CRS and acute swelling after sinus surgery in clinical practice.

Patients and methods

Patients

This study enrolled patients with a clinical diagnosis of CRS (as confirmed by CT of the paranasal sinuses in their medical history) who had to undergo sinus surgery. These patients may or may not have had nasal polyps (CRS+NP, CRS-NP). The patients' demographic data were collected on Day 0, and acute swelling after sinus surgery was confirmed by the physicians via endoscopy. To assess efficacy objectively, the physicians also rated oedema, rhinorrhoea and redness on a rhinoscopy score using a three-point scale (0 = absent, 1 = mild, 2 = severe) at all visits. Values were totalled to obtain the Total Rhinoscopy Score (TRS), as modified by Lund and Kennedy.[12] At Visits 1 and 5, the physicians also rated nasal polyps via endoscopic examination on a scale from 0 to 3 (0 = no polyps, 1 = small polyps (not extending beyond the lower edge of the middle concha), 2 = medium-sized polyps (extending beyond the lower edge of the middle concha, but not the lower edge of the inferior concha), 3 = large polyps (extending beyond the lower edge of the inferior concha)).

Study design and medication

This study was planned as a prospective, open-label observational pilot study. Its primary aim was to determine whether the clinical efficacy and tolerability of bromelain tablets (500 FIP) could be proven in a limited population of CRS patients who suffered from acute swelling after paranasal sinus surgery. Secondly, the thinking was that this pilot study would serve as a "preparatory study" for a possible subsequent prospective, randomised, placebo-controlled clinical trial. The pilot study was conducted in three centres from April to August 2011. Five visits took place during a treatment period of three months. In addition to an examination at the beginning of the study, follow-up examinations were conducted after 2, 5 and 8 weeks, and a final examination was performed after 12 weeks. The competent ethics committee was consulted with respect to professional regulations, and the study was conducted in accordance with Good Clinical Practice guidelines. Furthermore, informed consent was obtained from each patient.

The study investigated bromelain gastro-resistant tablets (500 FIP) manufactured by 'Ursapharm Arzneimittel GmbH', Saarbrücken, Germany. This medication has received approval for the treatment of acute swelling following surgery or injuries, especially of the nose and sinuses. FIP units are a measure of the enzyme activity of bromelain, which is determined by casein.[9] The daily dosage of bromelain tablets was based upon physicians' instructions, taking into account the recommendations on the packaging.

Evaluation of the course of symptom severity

To draw a conclusion about the effect of treatment with bromelain tablets (500 FIP), the Total Symptom Scores 4 and 5 (TSS 4 and TSS 5) were evaluated by the patients, and physicians assessed patient CRS at each visit using rhinoscopy. TSS 4 is based on the current clinical definition of rhinosinusitis/nasal polyps stated in EPOS 2007, which remained unchanged in EPOS 2012.[3] Each patient and corresponding investigator rated the severity of four symptoms caused by CRS (nasal obstruction, nasal discharge (anterior/posterior nasal drip), facial pain/pressure, and reduction of smell) at each visit.

In a recently published, double-blind, placebo-controlled study of the efficacy of mometasone furoate nasal spray (MFNS) in the treatment of CRS, a Total Symptom Score was used that included five CRS symptoms.[13] In order to compare the efficacy of bromelain with this nasal steroid, we also assessed TSS 5. Patients therefore recorded five CRS symptoms (rhinorrhoea, postnasal drip, nasal obstruction, facial pain or pressure, and headache) twice daily in a diary throughout the three-month treatment period. Symptom severity was rated on a four-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) for both scores, and then the Total Symptom Scores TSS 4 and TSS 5 were calculated

as the sum of the stated four or five CRS symptoms respectively.

Moreover, at the end of the treatment, the patients made a recommendation in favour of or against bromelain tablets (500 FIP).

Tolerability

Adverse events were recorded at each follow-up visit. At the end of the study, patients and investigators made a final evaluation of the tolerability of bromelain tablets.

Intake of bromelain 500 FIP tablets

The number and frequency of the tablets received were recorded daily in a diary. Patient compliance was therefore also documented.

Assessment of QoL (SNOT-20 GAV)

Using the rhinosinusitis-specific SNOT-20 GAV questionnaire translated into German by Baumann et al., it was possible to assess the impact of treatment with bromelain tablets (500 FIP) on QoL. Patients completed the SNOT-20 GAV on each of the five visits. The SNOT-20 GAV consists of 20 items indicating the severity of symptoms on a six-point scale (from 0 = no problem to 5 = no further worsening imaginable).[2] The overall score (OS) is the sum of the values of the 20 items.[14]

Statistical analysis

The statistical analysis was conducted using SPSS 19 for Windows. Double-data entry was performed in order to reduce data entry errors. Unavailable data were treated as 'missing values' or substituted using the 'last value carried forward' method for the evaluation of patient diaries. The obtained data were described as means ± empirical standard deviation for the total group and both subgroups CRS+NP and CRS-NP. The study protocol did not provide for a paired analysis.

Results

Twelve patients - seven women and five men - aged 25-63 years (mean 48.8 ± 10.2 years) were included in the pilot study. The enrolled patients had suffered from CRS for a mean of about 11 years. One patient dropped out of the study between Visits 4 and 5 due to an increase in discomfort, in particular nasal obstruction and sleep disturbance. All patients had undergone sinus surgery at least once, and nasal polyps were present in seven of the twelve cases.

The revised Table 1 offers an overview of both the type and the time of the performed paranasal surgery, as well as the patients' comorbidities. The manufacturer states that the pharmacological treatment of these comorbidities (antihypertensive and cholesterol-lowering drugs were most frequently

Table 1

Type and time of paranasal sinus surgery, and patient comorbidities

Patient ID	Type of Paranasal sinus surgery	Time of Paranasal sinus surgery	Comorbidities
1	Multiple pansinus operations	2010	Arterial hypertension
2	Maxillary sinus fenestration, Infundibulotomy on both sides	2011	Ø
3	Not specified	1990	Ø
4	Not specified	2010, 2008, 1995	Coronary heart disease
5	Not specified	2004	Bronchial asthma
6	Not specified	2005	Ø
7	Not specified	2010	HIV
8	Not specified	2009	Ø
9	Maxillary sinus fenestration, conchotomy	1990	Arterial hypertension
10	Nasal septal surgery, pansinus surgery	2010	Gastro-oesophageal reflux disease
11	Plastic septal correction, conchotomy, polypectomy	1984	Arterial hypertension, obstructive sleep apnoea syndrome
12	Not specified	2006	Ø

In all other cases, "endoscopic surgery of the paranasal sinuses" was performed without further specification.

Table 2
Intake of symptomatic medications during twelve months prior to the observational pilot study

Statistics \ Group		**Total** (12 patients)	**No polyps** (5 patients)	**Polyps** (7 patients)
Intake of symptomatic medication	N	10	4	6
	%	83.3	80	85.7
Eyedrops	N	2	1	1
	%	16.7	20.0	14.3
Nasal antihistamines	N	3	3	0
	%	25.0	60.0	0.0
Oral antihistamines	N	3	3	0
	%	25.0	60.0	0.0
Nasal corticosteroids	N	8	3	5
	%	66.7	60.0	71.4
Oral corticosteroids	N	4	2	2
	%	33.3	40.0	28.6
Bronchial corticosteroids	N	4	1	3
	%	33.3	20.0	42.9
Bronchial beta-sympathomimetic drugs	N	2	1	1
	%	16.7	20.0	14.3
Secretolytic medication	N	1	1	0
	%	8.3	20.0	0.0
NSAR	N	1	1	0
	%	8.3	20.0	0.0

prescribed) will not interact significantly with bromelain. (Ursapharm Arzneimittel GmbH. Expert Information on Bromelain-POS® [in German]. Ursapharm Arzneimittel GmbH, Saarbrücken, Germany, 2010.)

Concomitant medications for rhinosinusitis

Table 2 summarises the symptomatic drugs taken by the patients during the twelve months before the observational pilot study.

It was striking to note that eight out of twelve patients had taken nasal corticosteroids for symptom relief. All patients, however, denied having taken antibiotic substances.

Evaluation of the course of symptom severity

The mean value of TSS 4 for the total group at baseline was 5.53 ± 1.607, and 3.17 ± 2.304 after three months of treatment with bromelain tablets (500 FIP). In both subgroups, the mean TSS 4 decreased from Visit 1 to Visit 5 (CRS-NP: from 5.10 ± 1.808 to 2.08 ± 2.07; CRS+NP: 5.84 ± 1.512 to 4.08 ± 2.234), but the fall was first observed in CRS-NP patients rather than in CRS+NP patients (Figure 1). A clear difference was therefore observed between CRS+NP and CRS-NP.

Figure 2 shows changes from baseline in the all-day sum score for TSS 5 in the diaries. Over the total 86-day period, we found an improvement in the baseline-adjusted TSS 5 of 7.00 for CRS-NP patients and 2.14 for CRS+NP patients. The development also showed a clear difference between CRS-NP and CRS+NP patients. In both subgroups, a clear reduction in CRS symptoms was discernible after three weeks of treatment, although an inverse trend could be observed in CRS+NP patients after two months.

The effect of bromelain tablets (500 FIP) over a 12-week treatment period was confirmed by the reduction in the Total Rhinoscopy Score (TRS) for the total group from (mean) 3.42 to 1.36 after 12 weeks (CRS-NP: from 3.6 to 1.2, CRS+NP: from 3.29 to 1.5). In two patients with previously documented CRS+NP, polyps were no longer found after 12 weeks of treatment, and the grading ‘large polyps’ was no longer used in the group as a whole. At the end of the study, the majority of the

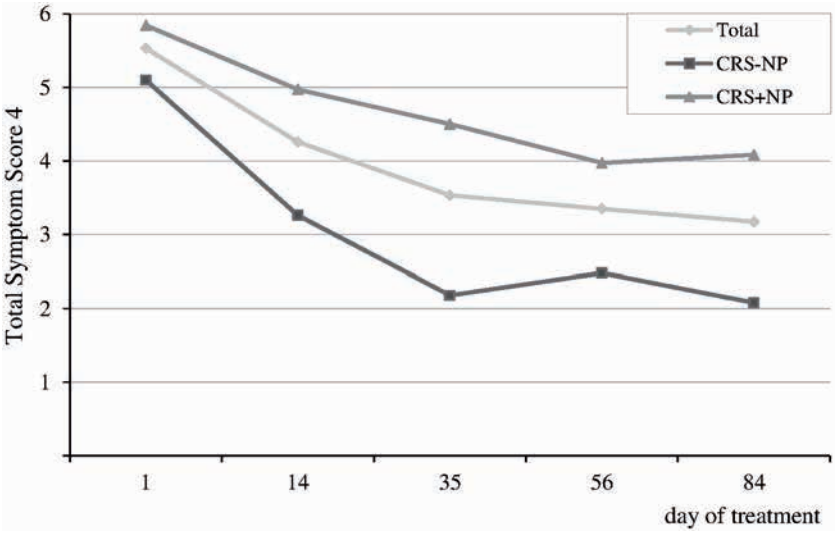

Figure 1
Development of the Total Symptom Score 4 (TSS 4). CRS-NP: chronic rhinosinusitis patients without nasal polyps; CRS+NP: chronic rhinosinusitis patients with nasal polyps; Total: total patients; TSS 4: Total Symptom Score 4.

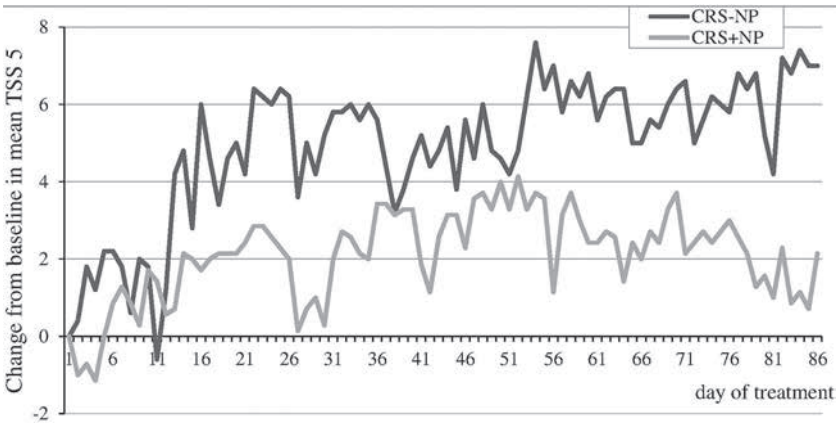

Figure 2
Improvement in the all-day sum score (mean) of the Total Symptom Score 5 (TSS 5) for CRS+NP and CRS-NP from baseline over 86 days. CRS-NP: chronic rhinosinusitis patients without nasal polyps; CRS+NP: chronic rhinosinusitis patients with nasal polyps; TSS 5: Total Symptom Score 5.

patients (54.5%) stated that they would certainly recommend bromelain tablets (500 FIP) and 9.1% said they would probably do so, whereas 36.4% would rather not recommend them.

Compliance

One patient took four tablets per day, while all the others took the recommended dose of six tablets daily during the entire observation period of three months, which indicates very good compliance.

Tolerability

All patients and investigators rated tolerability as 'good' or 'excellent' at the end of the study. The investigators did not document any drug-related adverse events.

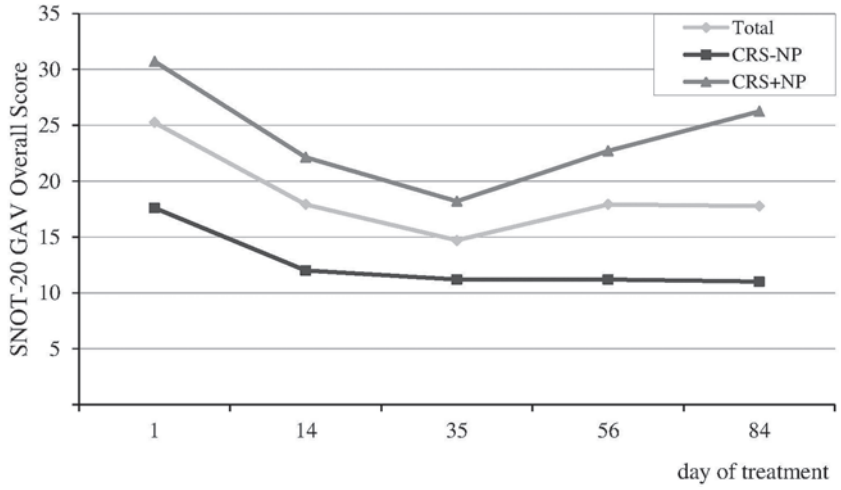

Figure 3
Development of the SNOT-20 GAV Overall Score. CRS-NP: chronic rhinosinusitis patients without nasal polyps; CRS+NP: chronic rhinosinusitis patients with nasal polyps; Total: total patients; SNOT-20 GAV: German, adapted version of the Sinonasal Outcome Test 20.

Quality of life

Both CRS+NP patients and CRS-NP patients achieved better SNOT-20 GAV scores during treatment with bromelain tablets (500 FIP). In CRS+NP patients the average impairment of QoL on the Overall Score at the beginning of the study and at the end was clearly higher. The OS indicated a fall in the mean value for CRS-NP patients from 17.60 to 11.00 points and from 30.71 to 26.25 points for CRS+NP patients. For the CRS+NP patient group, however, the mean OS initially dropped to 18.2 during the first 35 days of treatment and then deteriorated further to the final value of 26.25 (Figure 3).

Discussion

This pilot study was the first evaluation of the effect of bromelain tablets (500 FIP) on the course of symptom severity, tolerability, and QoL in the treatment of clinically and radiologically diagnosed CRS in clinical practice.

The results indicate that bromelain tablet (500 FIP) treatment is effective in improving patients' subjective symptom scores, and investigators' objectively rated rhinoscopy scores. These effects were observed for CRS-NP patients and CRS+NP patients alike after prior sinus surgery. Even the grading of nasal polyps could be improved in CRS+NP patients. The reports from patients about their personal perception of the severity of their symptoms were therefore also supported by objective parameters. In line with the improvements observed in this study, Taub *et al.*[10] and Seltzer *et al.*[11] have also found a reduction in rhinosinusitis symptoms in the presence of the adjuvant intake of bromelain. However, these investigations mainly looked at patients with acute rhinosinusitis. The reduction in rhinosinusitis symptoms is most likely due to the anti-inflammatory and oedema-reducing effects of bromelain.

TSS 4, TSS 5, and TRS all improved during treatment with bromelain tablets (500 FIP). Improvement was more marked in CRS-NP patients than in CRS+NP patients, but a reduction in polyp size was demonstrated by the results of the grading of the nasal polyps. The course of the baseline-adjusted all-day sum score, TSS 5, showed a downward trend for CRS+NP patients, which indicates a recurrence of CRS symptoms. Deal *et al.*[15] and Subramanian *et al.*[16] have already reported symptom relapse sooner and more often for CRS+NP patients than for CRS-NP patients, even after surgical[15] or intensive medical[16] CRS management.

Dudvarski *et al.*[17] reported that total symptom scores and endoscopy scores were similarly higher in CRS+NP patients than in CRS-NP patients. Deal *et al.*[15] also reported higher symptom scores, less improvement after surgical treatment, and poorer

objective findings for CRS+NP patients than for CRS-NP patients. A history of previous sinus surgery and the presence of nasal polyps are reported to be poor prognostic factors for the effectiveness of CRS management.[16,18] The improvement in CRS found in the present pilot study is therefore remarkable because all the patients underwent sinus surgery at least once and seven patients had CRS+NP.

CRS+NP is seen as a subgroup of CRS. However, it differs pathophysiologically from CRS-NP in several ways.[3] The most important pathophysiological dissimilarities include the different tissue types in the nasal polyps and the predominant type of inflammatory cells. The tissue of nasal polyps is frequently characterised by damaged epithelium, a thickened basal membrane, highly oedematous struma, and a small number of glands, blood vessels and nerve fibres. Inflammatory cells found here are (eosinophil) granulocytes, plasma cells, and activated T lymphocytes.[19,20] Accordingly, there are also differences in the constellation and severity of symptoms. Patients with CRS+NP therefore almost always suffer from the symptoms "nasal obstruction" and "reduction or complete loss of the sense of smell".[3,21]

The results of this observational pilot study also show that, the special pathophysiology of CRS+NP accounts for the fact that no perceivable improvement in CRS symptoms was observed despite bromelain tablet intake.

In principle, a placebo effect cannot be ruled out with certainty in this observational pilot study because of the absence of a control group. Establishing a control group, however, would interfere considerably with the design of an observational study. According to the German Medicinal Products Act and the regulations issued by the German superior federal authority, observational studies constitute "non-interventional" studies. One aim of an observational study is to acquire new knowledge about the course of treatment within an authorised indication in clinical practice (for bromelain 500 FIP tablets: acute swelling following surgery and injuries, particularly of the nose and paranasal sinuses (Ursapharm Arzneimittel GmbH. Expert Information on Bromelain-POS® [in German]. Ursapharm Arzneimittel GmbH, Saarbrücken, Germany, 2010)). Another principle underlying "non-interventional studies" is that physicians must not be influenced in their diagnostic and therapeutic decisions (here: free choice of pharmacotherapy for CRS).[22]

The majority of the patients could therefore be treated with other pharmaceuticals for CRS, first and foremost with nasal and oral steroids, in the twelve months before the pilot study. The intake of nasal and oral corticosteroids is consistent with the recommendations in the current EPOS guidelines from 2012.[3] All the more remarkable is the clear effect resulting from the intake of bromelain tablets (500 FIP) in spite of basic therapy with corticosteroids.

To compare the CRS symptom reduction induced by bromelain tablets (500 FIP) to that of a nasal steroid over an 86-day period, a double-blind, placebo-controlled study of the efficacy of MFNS can serve as a reference.[13] The course of the baseline-adjusted all-day sum score (mean) for TSS 5 indicates a distinct improvement after therapy both MFNS and bromelain tablets (500 FIP). The seven-point decrease in the baseline-adjusted mean value of bromelain tablets (500 FIP) for CRS-NP patients, as compared with the eight-point reduction of MFNS after 86 days, demonstrates that the efficacy of bromelain tablets (500 FIP) in this observational pilot study is similar to the nasal steroid (this is not a statistically significant finding).

Eleven patients took six tablets of bromelain tablets (500 FIP) daily, which is equivalent to a daily dosage of 3000 FIP units. One patient took only four bromelain tablets (2000 FIP units) daily during the entire observation period. In spite of this divergent study drug intake, systematic reviews confirm that the dose of bromelain is high enough.[8,9] There is therefore no reason to fear a loss of efficacy of the bromelain tablets. Tolerability was excellent, no AEs were observed, and the final assessments made by the patients and those made by the investigators were exclusively good or excellent. Correspondingly, patient compliance was very good. This may be due to the fact that bromelain is a phytotherapeutic drug that causes only few toxic side-effects, resulting in higher patient acceptance and compliance.[9]

QoL, as determined by the SNOT-20 GAV questionnaire, improved on average during and after three months of treatment, particularly in CRS-NP patients. OS in CRS+NP patients was clearly higher on average at the beginning and end of the study. CRS+NP patients in particular therefore feel that their QoL was impaired. Deal *et al*.[15] and

Banerji *et al*.[23] also regard nasal polyps as poor prognostic factors for the improvement of CRS symptoms on the SNOT-20 QoL questionnaire.

Conclusion

To summarise, bromelain tablet (500 FIP) treatment is a good additional treatment option for patients with CRS who have undergone previous sinus surgery. The treatment had a positive effect on patient symptom reduction and QoL. As expected, there was more average improvement in the symptom and rhinoscopy scores and on the QoL questionnaire in CRS-NP patients than in CRS+NP patients. CRS+NP is considered to be a subgroup of CRS,[3] yet the two groups have distinct symptom profiles[23,24] and respond differently to therapy.[24] The differences between the CRS+NP and CRS-NP groups observed after and during treatment with bromelain tablets (500 FIP) are clearly visible in Figures 1 to 3. Tolerability was good, and no adverse reactions were observed during the treatment period.

Although the results of this pilot study are very promising with respect to efficacy, tolerability and QoL, further studies are needed to validate these findings.

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