Controlled Double-Blind Study of a Homeopathic Sinusitis Medication

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Summary

Topic: Investigation of the clinical effectiveness of Euphorbium compositum S Nasal Spray in therapy of chronic sinusitis.

Design: Randomized, placebo controlled, double-blind study over a five-month period.

Subject/Collective: Solely such subjects were included in this study as suffered from established, chronically recurrent - although not acute - rhinosinusitis, for whom conservative therapy was indicated during symptom-free intervals. Excluded from the study, among others, were patients who smoked, suffered from nasoendoscopically confirmed polyposis or infectious rhinitis, were known to possess unhealed apical granulomata, whose cases of sinusitis were established to be odontogenous, or had undergone surgical treatment within the previous six months. The investigation encompassed a total of 172 patients, 155 of whom were included in the final evaluation (89.6 %).

Intervention: 2 discharges of verum or placebo respectively into each nostril 4 times daily over a period of five months.

Chief Objective Variables: For the purpose of statistical comparison among the therapeutic groups, a cumulative score was calculated from the data compiled in the three sectors "Subjective Symptoms (day/night)", "Anterior Rhinoscopy", and "Ultrasound Examination of the Paranasal Sinus".

Results: Statistical comparison of the therapeutic collectives demonstrates significant superiority of Euphorbium compositum S Nasal Spray (5 % significance level, p = 0.016). Improvement was most evident within the subjective criteria of respiratory obstruction, sensation of pressure, and headache. Euphorbium compositum S Nasal Spray was well tolerated.

Conclusions: This study substantiates the reliable efficacy and good tolerance of Euphorbium compositum S Nasal Spray in therapy of chronic sinusitis. In addition, it demonstrates maintenance of a high standard of methods and acquirement of meaningful test results to indeed be feasible in homeopathy.

Key Words: Euphorbium compositum-Nasentropfen S, chronic sinusitis, double-blind study

1. Introduction

Chronic sinusitis is a syndrome of multifactorial origin. Autonomous in regard to acute sinusitis, it frequently acquires clinical significance for the patient through symptoms displayed during phases of acute exacerbation [1]. Clinical symptoms of sinusitis include general fatigue, headache, facial pain, inhibited nasal respiration, and secretory discharge into the pharynx. Pathophysiological manifestations are edematous swelling of the mucous membranes, the formation of retention cysts, and polyposis. The most frequent cause of sinusitis is infection conveyed from the nasal cavity (e.g. through streptococci or staphylococci). Development may be promoted by such factors as hyperplasia of the nasal conchae, deviation of the septum, and rhinopolypi. The following diagnostic techniques are generally employed: rhinoscopy, ultrasound, radiography (opacity of the maxillary sinus), sinuscopy, exploratory puncture or biopsy, and bacterial analysis of secreted matter. As a rule, medicinal therapy of sinusitis consists of administering detumescent nasal drops (rhinological agents) and possibly antibiotic drugs. Physical treatment includes such techniques as thermotherapy and sinus puncture.

Euphorbium compositum S Nasal Spray (manufacturer: Biologische Heilmittel Heel GmbH) is a homeopathic rhinological preparation which, due to the symptom pictures of its individual constituents, is employed in treatment of rhinitis, chronic sinusitis, and other related affections. Through promoting mucosal function, this preparation exerts regulative action on the various diseases affecting paranasal mucosae. The reliable effectiveness and excellent tolerance of Euphorbium compositum S Nasal Spray has been confirmed in numerous application studies and reports of practical experience [2,3,4]. To date, however, no placebo-controlled, double-blind clinical study has been performed utilizing Euphorbium compositum S Nasal Spray for the indication of "chronic sinusitis". The objective of this clinical investigation, therefore, was to ascertain scientific proof of efficacy.

2. Method

This investigation was conducted as a multicentric, double-blind, parallel group-comparison study (verum vs. placebo). A total of eleven E-N-T physicians with private practices participated in the study. In this investigation, two verum preparations were to be evaluated in regard to their effectiveness: Euphorbium compositum S Nasal Spray (ECN1) and a version of Euphorbium compositum containing a reduced number of constituents

(ECN2). Treatment data and examination findings were documented by the participating physicians on forms developed expressly for this purpose. The study design was chosen as described for the purpose of avoiding any bias through patients or investigating physicians, as well as to assure equal distribution of any undetermined factors of interference among the three subject collectives. This study was conducted in accordance with the Principles of Good Clinical Practice [5]

2.1. Patient Selection

The comparative study "ECN1/ECN2 vs. Placebo" solely included such patients (males and females above the age of 18 years) as were affected by established, chronically recurrent - although not acute - rhinosinusitis, for whom conservative therapy was indicated during symptom-free intervals. A minimum of three episodes of sinusitis were to have occurred during the year prior to study commencement, or at least four episodes of sinusitis over a period of the previous three years, or the patient was to be currently experiencing constant discharge of secretion within the nasopharyngeal region. In the interest of differential diagnostics, at least one criterion was to be met in each of two fields for ascertaining requirement of conservative therapy: one subjective criterion (respiratory blockage, rhinorrhea, headache, sensation of pressure) as well as one ultrasound criterion (extensive anterior-wall echo, cysts, and fluids). Excluded from the study were such patients who:

- utilized tobacco products,
- suffered from nasoendoscopically confirmed polyposis,
- displayed opacity of the ethmoid bone in conventional radiodiagnostic examination,
- were known to possess unhealed apical granulomata,
- whose cases of sinusitis were established to be odontogenous,
- were affected by infectious rhinitis,
- had undergone surgical treatment in the previous six months,
- simultaneously utilized additional medications in treating their chronic sinusitis (particularly antibiotic and antiinflammatory agents),
- employed medication in therapy of further affections which may have influenced the nasal mucosae,
- were known to be allergic to the preservative agent benzalkonium chloride,
- had participated in any other clinical study within the previous four weeks,
- as well as female patients who were pregnant, nursing, or with insufficient contraception.

2.2. Procedure

The study was conducted in the Federal Republic of Germany from April 1990 to August of 1993. The investigation consisted of an initial phase of four weeks, during which any improvement in the symptom complex was to be ascertained in two control examinations, and a follow-up period of four months, which served to determine the interval of time prior to recurrence. The following data was recorded during the initial examination in addition to demographic information: duration of illness, number of sinusitis episodes during the previous year/three years (whichever was applicable), presence of headache and congestion of the head, date of the most recent episode of acute sinusitis, as well as presence of any olfactory impairment and its time of onset. Concomitant illnesses and accompanying therapies were also registered. In order to trace the course of the affection, the parameters shown in Table 1 were recorded at the beginning of the study, subsequent to two and four weeks' treatment each, as well as at the conclusion of the four-month follow-up period. In cases in which recurrence took place prematurely (during the follow-up period of four months), the findings were documented at that point and the study of that patient terminated.

On concluding treatment of each case, both patient and attending physician submitted closing evaluations of the test medication on two points: the degree of therapeutic success (scale: excellent, good, satisfactory, or insufficient), as well as the degree of tolerance (scale: excellent, good, moderate, or poor). Any undesirable effects, whether observed by the physician or spontaneously related by the patient, were to be documented in their entirety on the investigation form, regardless of any possible relevance to the test medication.

2.3. Study-Objective Criteria

For the purpose of statistical comparison of the three subject collectives, a cumulative score (= chief objective criterion) was calculated from the data compiled in the three sectors "Subjective Symptoms (day/night)", "Anterior Rhinoscopy", and "Ultrasound Examination of the Paranasal Sinus". The cumulative score was calculated according to the following procedure: First, the responses within the three indicated areas were coded by means of an ordinal scale. The value 1 was invariably assigned to symptoms documented as absent. The presence of bipartite symptoms (e.g. Sensation of Pressure: "yes") was coded with the value 2. In calculating symptoms consisting of four sub-sectors, each positive response was coded with the value 2, 3, or 4, corresponding to three distinctive stages of increasing severity. For each of the three above-indicated sectors, the sum of the response-codes was determined and the result subsequently divided by the number of parameters in that sector. In the section indicating subjective symptoms, therefore, the sums were divided by eight (four symptoms, each day/night); the sums reflecting the parameters of anterior rhinoscopy were divided by six. As the parameters in reference to ultrasound examination of the paranasal sinus were inapplicable in certain cases (on absence of posterior-wall echo), this mean value was calculated on the basis of the actual number of responses submitted. The three averages deter-

mined in this manner were then added and their sum divided by three, thus yielding the cumulative score. Theoretically, this score could assume a value ranging from 1 (= no findings whatsoever) to 2.6 (maximum findings in all parameters). Secondary criteria consisted of endoscopic findings as well as continuous data from initial treatment to the incidence of first recurrence (long-term results).

2.4. Statistics

In order to determine appropriate volume for random testing, calculation was performed on the basis of the total number of cases. Under consideration of the level of significance, test strength, and an increased response rate of 30 % under verum therapy, calculation indicated a random-test volume of 50 patients per group. Randomization of the patients (block size = 10) to one of the three therapeutic collectives was carried out with the aid of a computer program (Rancode, IDV Co. / Munich). No stratification was performed. The code was known only to the responsible biometric specialist. In accordance with GCP regulations, each investigating physician was provided with sealed envelopes for emergency use at study commencement. The code was broken in three cases during the course of this study due to intolerable side effects (ECN1-group: 2 cases, ECN2-group: one case). In all remaining cases, the code was deciphered only after completion of the investigation, i.e. at the beginning of evaluation.

Objective of this clinical study was to provide scientific proof of the effectiveness of ECN1 and/or ECN2 in treatment of chronic sinusitis, i.e. proof of significant superiority of ECN1 and/or ECN2 over the placebo. Equal findings among the three therapeutic groups, therefore, was defined as the global null hypothesis (global significance level = 5 %). Each of the adopted parameters was descriptively evaluated in accordance with its symptom type. For data rated on nominal and ordinal scales, frequency was tallied and collectively tabulated using percentage values. Base statistics were established for symptoms rated on an interval scale. The Jonckheere test was utilized in examining the global hypothesis, the Mann-Whitney U-test and Wei-Lachin analysis were applied in conducting individual comparisons among the collectives [6]. The long-term findings were assessed by means of "survival-time analysis" according to Kaplan-Meier (for patients experiencing no recurrence, the entire duration of therapy was included). All indicated statistic tests were unilaterally applied. The investigation was evaluated in accordance with the "Intent to Treat" principles.

Subjective Symptoms (day/night):	**Anterior Rhinoscopy:**
Respiratory obstruction	Hyperplasia of the inferior concha
Rhinorrhea	Alteration of the mucosa
Headache	Alteration of secretion
Sensation of pressure	
Ultrasound Examination of the Paranasal Sinus:	**Endoscopy of the Nose:**
Extensive anterior-wall echo	Ostia
Posterior-wall echo	Pathological secretion
Cysts	Terminus of the inferior concha
Fluids	Condition of the concha media
	Contact with septum

Table 1: Parameters Recorded for the Purpose of Monitoring Pathological Progress

2.5. Test Preparations and Dosage

The composition of the test preparations ECN1 and ECN2 is presented in Table 2. The placebo consisted of isotonic sodium-chloride solution (containing 0.01 % benzalkonium chloride). Neither patients nor physicians could identify the various test medications, as the scent, taste, appearance, and packaging of these test preparations were identical. Patients and physicians were enjoined to refrain from discussing group membership, both between physician and patient as well as among the patients themselves. The possibility of such contacts having actually been made in isolated cases, however, cannot ultimately be excluded with absolute certainty.

The test medications were prepared in accordance with GMP Regulations, filled into single-dosage atomizers of 20 ml capacity, and temporarily stored in a locked chamber. The preparations were coded according to the randomizing list under observation of GCP Regulations. Each atomizer was duly marked with the required compulsory data. The appropriate medication was distributed to each patient on his or her initial examination, and the consumed quantity recorded at each subsequent control examination. During the initial four-week phase and the ensuing four-month follow-up period, a dosage of 2 discharges were to be sprayed into each nostril 4 times daily.

3. Results

For reasons of general clarity and comprehension, detailed description of the therapeutic results of ECN2 has been waived in the subsequent sections.

3.1. Patient Collectives

Of the 173 patients originally participating in the study, 155 could be included in the final evaluation. An audit performed during the initial phase of the study revealed one participating center to have submitted no original data whatsoever. Thus un-

suitable for utilization, the information recorded on these 18 subjects (group membership: 6 patients each from the ECN1, ECN2, and placebo collectives) was consequently excluded from final evaluation procedures. No apparent differences existed among the three patient collectives in regard to base data, i.e. age, gender, olfactory disturbance, duration of affection, number of sinusitis episodes, degree of headache and congestive severity, interval since last episode of sinusitis, concomitant affections, and accompanying therapies (Table 3).

3.2. Therapeutic Procedure

The initial phase of the ECN1-group averaged 30 days (+/-8) in duration, with that of the placebo-group averaging 31 days (+/-10). The mean total length of therapy was 148 (+/- 44) days in the ECN1-group and 151 (+/- 30) days in the placebo collective. Per-patient consumption of test medication during the initial phase averaged 36.1 ml in the ECN1-collective, and 35.6 ml in the group having received the placebo.

3.3. Chief Objective Criterion

In accordance with the investigation schedule, the symptom complex was monitored at the beginning of the study (= initial examination), subsequent to two weeks of treatment (= 1st control examination), as well as ensuing four weeks' therapy (= 2nd control examination). The results of these examinations are presented in Table 4.

As these data demonstrate, both groups registered general improvement within their symptom complexes during the course of treatment in all monitored criteria (excepting that of "cysts"). From a clinical aspect, the most significant alterations occurred in the criteria "Respiratory Obstruction (night)" (p = 0.0047), "Respiratory Obstruction (day)" (p = 0.0265), "Sensation of Pressure (day)" (p = 0.0518), and "Headache (night)" (p = 0.0760). On the basis of the patients' subjective assessments and apparatus readings, a cumulative score was calculated for each patient collective. Over the course of the therapeutic period, the mean cumulative score of the ECN1-group improved from 1.75 +/- 0.29 (initial examination) to a value of 1.37 +/- 0.30 (final examination). This corresponds to an average improvement in the symptom complex of 21.1 %. The cumulative score for the placebo-collective improved from 1.71 +/- 0.28 (initial examination) to 1.44 +/- 0.34 (final examination); (mean reduction = 14.3 %). Thus global improvement in the cumulative score, i.e. in the symptom complex, was detectable in both therapeutic groups. Statistical evaluation of the data shows that, with a 5 % significance level, the null hypothesis (equality of absolute improvement) is to be rejected (p = 0.016). Individual comparison among the collectives by means of a centrally-adjusted U-test according to Mann-Whitney demonstrates the superiority of ECN1 vs. placebo ($P_{unilateral}$ = 0.015) (Tab. 5). No significant difference was demonstrated on comparing ECN2 versus the placebo ($P_{unilateral}$ = 0.130), as was the case upon comparing the two verum preparations ($P_{unilateral}$ = 0.145).

Constituents	ECN1	ECN2
Euphorbium	D 4 (1 ml)	D 6 (1ml)
Pulsatilla	D 2 (1 ml)	D 3 (10 ml)
Luffa operculata	D 2 (1 ml)	D 3 (10 ml)
Mercurius bijodatus (mercuric biniodide)	D 8 (1 ml)	-
Mucosa nasalis suis	D 8 (1 ml)	-
Hepar sulfuris	D10 (1 ml)	D 10 (1 ml)
Argentum nitricum (silver nitrate)	D10 (1 ml)	-
Sinusitis-Nosode	D13 (1 ml)	-
Benzalkoniumchlorid (benzalkonium chloride)	0.01 %	0.01 %

Table 2: Composition of the Test Preparations ECN1 and ECN2 (Diluting Solution: Isotonic Sodium-Chloride Solution)

Above all else within a symptom complex, it is precisely the field of subjective discomfort which is of particular importance to the sinusitis patient. As the most significant clinically relevant alterations were observed within this sector (see above), an additional cumulative score was calculated for each therapeutic group regarding the criterion "Subjective Symptoms" subsequent to study conclusion (this post-hoc analysis had not been planned in the original investigation schedule). Statistic comparison of the collectives by means of a U-test showed significant differentiation between ECN1 and placebo (p = 0.0105) (ECN2 vs. placebo: p = 0.0379; ECN1 vs. ECN2: p = 0.237).

3.4. Secondary Criteria

Endoscopic examination conducted at the conclusion of the initial phase showed general improvement of the symptom complex in both the ECN1 and placebo collectives. The most distinct improvement in both groups was noted in the criteria "Condition of the Concha Media" and "Contact with Septum". At commencement of therapy, the score in both collectives measured approx. 1.3. By the close of the initial phase, this value was reduced by an average of 9.5 % in the ECN1 group, and 9.1 % in the placebo collective (ECN2 group: -8.8 %). In regard to the secondary criterion "Nasal Endoscopy", however, no statistically-significant difference existed between the two groups (Table 6).

Data regarding long-term study (= interval prior to first recurrence or, in recurrence-free cases, the total duration of treatment) was evaluated employing the method of "Survival-Time Analysis" according to Kaplan-Meier.

Description/Symptoms	ECN1-Gr.	ECN2-Gr.	Placebo-Gr.
Number of Patients	53	51	51
Age (years)*	43.2±13.9	44.9±13.7	44.0±14.8
minimum/maximum	19/70	19/76	19/74
Gender			
male	20 (38%)	17(33%)	21(41%)
female	33 (62%)	34 (67%)	30 (59%)
Olfactory Disturbances			
number	6 (11%)	6 (12%)	8 (16%)
duration (years)**	1.8	4.1	2.7
Duration of Illness (years)**	5.5	4.0	4.0
Number of Sinusitis Episodes			
during previous years**	4±1	4±1	4±1
during previous 3 years**	9±3	9±3	10±3
Headaches			
none	7 (13%)	7 (14%)	8 (16%)
seldom	19 (36%)	21 (41%)	23(45%)
frequent	27 (51%)	23 (45%)	20 (39%)
Head Congestion/Pressure			
none	7 (13%)	6 (12%)	8 (16%)
seldom	19 (36%)	20 (39%)	19 (37%)
frequent	27 (51%)	25 (49%)	24 (47%)
Interval since Last Sinusitis Episode (days)**	47	72	89
Concomitant Affections	3 (6%)	8 (16%)	5 (10%)
Type of Affection	1 Bronchitis	3 Hypertonia	1 CS-Syndrome
(multiple indications possible)	1 Gastritis	1 Epilepsy	1 Polyarthritis
	1 Migraine	1 Prostate	1 Hypotonia
	1 Asthma	complaints	1 Cystitis
		1 Thrombosis	1 Estrogen
		1 Hypotonia	deficiencies
		2 Strumata	
		1 Hypothyroidism	
Accompanying Therapies	2 (4%)	7 (14%)	4(8%)
Type of therapy	1 Gaviscon	2 Beloc	1 Sinupret
(multiple indications possible)	1 Antacida	1 Valpromin	1 Doxy
	1 Ibuprofen	1 Marcumar	1 Euthyrox
	1 Eudur	1 Euthyrox	1 Spasmo-Urgenin
		1 Catapresen	1 Ortho-Urgenin

*Table 3: Anamnestic Data of the Three Patient Groups (number of patients is indicated; * = mean value +/- standard deviation; ** = median)*

Results showed that with a 5 % significance level, probability-distribution of recurrence-free intervals is to be viewed as non-differential for the patients of both collectives, i.e. no difference existed between the two groups in respect to this criterion.

3.5. Undesirable Medicinal Effects

Within the three therapeutic collectives, undesirable medicinal effects were documented in a total of five cases. One subject in the ECN1 group reported swelling, a burning sensation in the nasal region, as well as reddening of facial skin. A further patient of this collective complained of drowsiness, excitation, trembling, and congestion. One subject belonging to the ECN2 group reported dizziness, a further patient of the same collective complained of watering eyes. One case of herpes zoster was documented in the placebo group. In none of the cases did investivating physicians definitively establish the undesired effects

	ECN1 Group n = 53			Placebo Group n = 51		
	Findings Present on Commencement[1]	Findings Present or Improved on[2] 1stContr.	2ndContr.	Findings Present on Commencement[1]	Findings Present or Improved on[2] 1stContr.	2ndContr.
Subjective Symptoms:						
Respiratory obstruction (day)	73.6	58.9	41.1	78.4	67.5	60.0
Respiratory obstruction (night)	79.2	54.7	33.4	76.5	58.9	51.3
Rhinorrhea (day)[3]	60.4	62.5	46.9	70.6	61.1	47.2
Rhinorrhea (night)[3]	43.4	69.6	47.8	41.2	66.7	66.7
Headache (day)[3]	49.1	50.0	50.0	49.0	60.0	48.0
Headache (night)[3]	39.6	42.9	28.6	37.3	52.6	36.8
Sensation of Pressure (day)[3]	71.7	52.6	39.5	52.9	74.1	40.7
Sensation of Pressure (night)[3]	54.7	51.7	31.0	45.1	52.2	30.4
Anterior Rhinoscopy:						
Hyperplasia of inf. concha[4]	73.6	69.2	53.9	70.6	63.9	41.7
Alteration of mucosa[4]	92.5	48.9	42.9	90.2	58.7	34.7
Alteration of secretion[4]	69.8	48.7	29.7	62.7	46.9	31.2
Ultrasound of Paranasal Sinus:						
Extensive anterior-wall echo[4]	77.3	73.1	53.6	72.5	81.1	59.5
Posterior-wall echo[4]	22.6	75.0	66.6	21.6	72.7	72.7
Cysts[4]	9.5	100.0	100.0	13.7	100.0	100.0
Fluids[4]	15.1	87.5	62.5	9.8	80.0	80.0

Table 4: Alterations within the Subcriteria of the Chief Objective Variables during the Four-Week Initial Phase (Data in percent: 1 = percentile of the therapeutic collective; 2 = percentile of patients with pathological findings at commencement of therapy; 3 = permanently dispelled on change; 4 = mean value of right and left side; Improvement = initially present on both, subsequently on one side; 1stContr. = 1st control examination ensuing two weeks' therapy; 2ndContr. = 2nd control examination ensuing four weeks' therapy, i.e. at conclusion of initial phase).

to stand in relationship with the test medication. The side effects remained without consequence in all five cases, with the patient's status assessed at closing of therapy as either "re-established" or "improved". These reported side effects notwithstanding, 90 % of the investigating physicians and patients of the ECN1 collective, 94 % in the ENC2 group, and 97 % in the placebo group provided the tolerance of the test preparations with a rating of "excellent" to "good". Two subjects in the ECN1 collective evaluated tolerance as "poor" (ECN2 group: two patients and one physician made the assessment "poor.")

3.6. Discontinuation of Therapy

Nine subjects in the ECN1 group prematurely discontinued participation in the study. The grounds indicated were: insufficient compliance (four patients), undesired medicinal effects (two patients), no improvement of the symptom complex (one patient), headache in accompaniment of cervical-spine syndrome (one patient), as well as scheduling difficulties (one patient). In the collective treated with ECN2, six subjects abandoned the study at a point earlier than planned for the following reasons: recurrence (two cases), intercurrent affections (two

	ECN1 Group n = 53				Placebo Group n = 51			
	MV+/-SD	Min.	Max.	Med.	MV+/-SD	Min.	Max.	Med.
Initial Examination	1.75±0.29	1.11	2.49	1.75	1.71±0.28	1.11	2.22	1.71
1st Control Examination	1.50±0.29	1.00	2.29	1.43	1.55±.029	1.22	2.22	1.51
2nd Control Examination	1.37±0.30*	1.00	2.10	1.32	1.44±0.34	1.00	2.31	1.35

*Table 5: Alteration of the Cumulative Score (Chief—Objective Criterion) during the Four-Week Initial Phase (MV +/- SD = mean value +/- standard deviation; * = p = 0.015; Min. = minimum; Max. = maximum; Med. = median).*

	ECN1 Group n = 53		Placebo Group n = 51	
	Findings present on commencement[1]	Findings present or improved on treatment[2]	Findings present on commencement[1]	Findings present or improved on treatment[2]
Obstruction of ostia[3]	41.5	40.9	45 1	39.1
Pathological secretion[3]	47.1	40.0	45.1	43.5
Terminus of inferior concha (enlarged)[3]	49.1	65.4	52.9	66.7
Condition of concha media (edamatous)[3]	49.1	19.2	54.9	35.7
Contact with septum[3]	20.8	36.4	35.3	22.2

Table 6: Alterations in the Secondary Criterion "Nasal Endoscopy" during the Initial Phase (Data in percent: 1 = percentile of the collective; 2 = percentile of patients with pathological findings at commencement of therapy; 3 = mean value of right and left side)

cases), undesired medicinal effects (one case), as well as on the miscellaneous grounds of "subjectively unpleasant taste" (one case). Of the placebo-group, nine subjects discontinued participation. The grounds for abandonment were recurrence (one patient), intercurrent affection (one patient), insufficient compliance (four patients), relevant worsening in findings (one patient), lack of symptoms (one patient), and therapeutic failure (one patient).

3.7. Evaluation of Efficacy

On conclusion of the five-month therapeutic period, or correspondingly earlier in cases experiencing recurrence, the effectiveness of each treatment was evaluated by the investigating physician and patient involved. (As variation between the physicians' assessments and those indicated by the patients was negligible, separate illustration was waived in presenting the results.) In the ECN1 and placebo groups, therapeutic efficacy was rated "excellent" to "good" in over 60 % of the cases. A global assessment of "insufficient" was indicated in every 5th treatment of the ECN1 group, and in every 7th therapy of the placebo selective (Fig. 1).

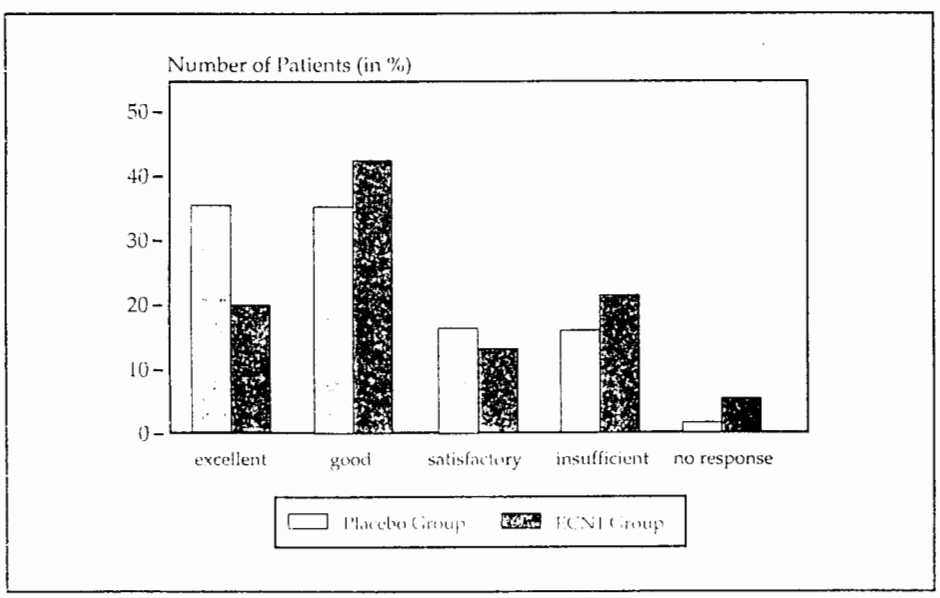

Fig. 1: Global Evaluation of Therapy (Placebo Group: n = 51; ECN1 Group: n = 53).

4. Discussion

To those affected, chronic sinusitis is generally an unpleasant and annoying disorder. For this reason, an effective yet low-risk method of therapy is particularly desirable. Due to the symptom-pictures of its individual constituents, the homeopathic rhinological preparation Euphorbium compositum S Nasal Spray is indicated in treatment of chronic sinusitis. The objective of the clinical study in hand was to provide scientific substantiation of the effectiveness of Euphorbium compositum S Nasal Spray in patients suffering from chronic sinusitis, as well as to investigate its tolerance. This study has proven the efficacy of that agent. Statistical comparison of the therapeutic collectives ECN1 vs. placebo demonstrates significant superiority of the homeopathic rhinological preparation. This superiority is greatest in the subjective parameters of respiratory obstruction, sensation of pressure, and headache. These findings are particularly significant, as improvement in precisely this sector of the symptom complex is of primary interest to the patient. Although the p-values calculated are suited for descriptive interpretation only, they nevertheless illustrate the most important clinical alterations which occur under therapy employing Euphorbium compositum S Nasal Spray.

As anticipated, a number of patients from the placebo-collective also rated

the overall therapeutic effectiveness as good to excellent. This fact is optically represented in Figure 1. These positive evaluations may well be ascribable to the circumstance that the placebo employed in this study (physiological saline solution) actually constitutes a medicinal agent in itself, thus being therapeutically active. In pediatrics, for example, saline solution is frequently employed in successful treatment of sinusitis. Spray application of saline solution partially cleanses crustose matter and secretion from the nasal region, in addition to reducing dryness of nasal mucosa, a symptom patients experience as particularly unpleasant. Yet nevertheless, evidence of the verum's therapeutic superiority to this "placebo" is documented in the significantly greater degree of alteration observed in the subcriteria of the chief objective variables. The "inconsistency" of many placebo-subjects' globally evaluating treatment as good to excellent, yet on the other hand assigning poor ratings to the various subcriteria, may reflect a methodic flaw. When questions are formulated in an excessively generalized manner, the subjects apparently tend toward a more positive evaluation of their health statuses. It is not currently possible to assess reproductability of the described findings, as this study is the first of its kind. Relevant literature, however, contains numerous accounts of investigations (application-survey studies and reports of practical experience) which confirm the results of this investigation.

With the aid of a multicentric application-study, Zenner and Metelmann [4] documented therapeutic data concerning the administration, effectiveness, and tolerance of Euphorbium compositum S Nasal Spray. A total of 3510 patients suffering from rhinitis, acute sinusitis, chronic sinusitis, or other related affections were included in this study. Final therapeutic evaluation indicated 73 % of the subjects with chronic sinusitis (n = 509) assessed treatment employing the homeopathic rhinological preparation as "excellent" to "good". The application-study additionally confirmed this medicinal combination preparation to be well tolerated, an empiric observation long-since recognized. Sprenger [3] described 94 cases utilizing Euphorbium compositum Nasal Spray in treatment of acute and chronically-recurrent rhinitis, rhinitis with various concomitant affections, as well as sinusitis. "Good" therapeutic results were achieved in 81 % of the cases, with 9 % experiencing "moderate" success. In merely 10 % of the cases was therapy unsuccessful. The medication was tolerated excellently to well, with no cases of intolerance observed. In an investigation conducted by Connert and Maiwald [2] under omission of placebo control, evidence was found suggesting long-term application of Euphorbium compositum Nasal Spray to be indicated in treatment of chronic-medicinal and vasomotorically-induced cases of rhinopathy. In their examinations conducted on a select patient-collective, rhinomanometric measurement of air-flow resistance during nasal respiration served as an objective symptom of alteration in nasal patency. A total of 51 patients were included in the study, in whom impaired nasal respiration was manifest for a minimum of six months prior to commencement of therapy (dosage: 2 discharges of spray per nostril, 3 X daily). Evaluation of the readings showed a statistically significant reduction in the degree of resistance during nasal respiration resulting from therapy employing the homeopathic rhinological preparation. The medication was tolerated free of side effects in all subjects, and was readily accepted due to its pleasant mode of application.

The findings of the study in hand substantiate the statistical superiority of the verum to the placebo. To what extent, however, is this superiority clinically relevant? Euphorbium compositum S Nasal Spray may be viewed as an alternative to chemically-defined preparations. Particularly advantageous in long-term therapy of chronic sinusitis, it is well tolerated and free of the potential side effects inherent to preparations containing drugs such as ephedrine, for example, which may cause circulatory disturbance, mucosal atrophy, and rebound effects. Neither habituation nor effects of acquired tolerance are to be expected through application of Euphorbium compositum S Nasal Spray.

In addition to the reliable efficacy and excellent tolerance of Euphorbium compositum S Nasal Spray, this study also proves maintenance of a high standard of methods and acquirement of meaningful findings to indeed be feasible in homeopathy [7]. Moreover, any possibility of systematic bias has been extensively precluded through strict adherence to the GCP principles and the chosen study design.

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