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ORIGINAL ARTICLE

Kinetic oscillation stimulation as treatment of non-allergic rhinitis: an RCT study

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Abstract

Conclusion: Kinetic oscillation stimulation (KOS) of nasal mucosa at low frequency seems to be a possibly effective and safe short-term treatment of non-allergic nasal stuffiness. *Objective:* To assess the relief of rhinitis symptoms, especially stuffiness, by comparing active treatment, i.e. KOS at low frequency of the nasal mucosa, with placebo. *Methods:* Patients were randomized to active or placebo treatment in this double-blinded parallel design study. Treatment with an inflatable oscillating catheter was administered on day 0, and symptom scores (stuffiness, secretion, and itching) were graded daily until day 14. An overall grading of symptoms from 1 week before treatment and during 14 days thereafter was made at day 14. Eighty-six patients (52 with non-allergic perennial rhinitis, NAR; 34 with rhinitis medicamentosa, RM) were randomized, and 71 were evaluated (active treatment, $n = 35$; placebo, $n = 36$). *Results:* Patients with either NAR or RM who received active treatment reported reduced symptom scores by some measures, e.g. median RQSS stuffiness measure fell from 2 to 1 on a scale from 0 to 3 during the week following treatment. No significant effect was observed for patients treated with placebo. Mild side effects were reported.

Keywords: *Idiopathic rhinitis, vasomotor rhinitis, rhinitis medicamentosa, stuffiness, minimally invasive, low frequency nerve stimulation, neuromodulation, medical device, autonomic nervous system*

Introduction

Rhinitis is common in outpatient settings [1]. Patients with allergic rhinitis get symptomatic relief from anti-allergic treatment such as steroid nasal sprays. However, many patients with persistent rhinitis have no identifiable etiology and a negative outcome in allergy tests. These patients, classified as having non-allergic perennial rhinitis (NAR), often describe stuffiness as the most troublesome symptom and the relief gained with anti-allergic treatment, such as steroid spray, is unsatisfactory [1]. Some patients with therapy-resistant NAR, as well as patients with rhinitis medicamentosa (RM), are effectively addicted to vasoconstrictors in a vicious circle of overuse and rebound effects [2]. The unclear pathogenesis of NAR and RM, and the absence of reliable immunological markers, make the interactions between the immune and nervous systems of interest in these patients [1,3–6].

In a healthy nasal cavity the airflow is sensed by the nervous system. An inflammatory process could lead to mucosal swelling, which in turn could potentially prevent the nervous system from detecting the airflow passing over the surface. The idea behind the kinetic oscillation stimulation (KOS) treatment investigated in the present study was that perhaps applying mechanical oscillations similar to naturally occurring turbulence would have a positive effect on the inflammatory ondition in the mucosal surface layer.

The aim of this blinded placebo-controlled parallel study was to investigate if KOS treatment, i.e. low frequency, low amplitude vibrations applied to the nasal mucosa surface for several minutes, could reduce rhinitis symptoms, most notably the sensation of stuffiness, in patients with either NAR or RM, specifically for

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rhinitis patients without allergic or infectious origin. Symptom scores were the main study variables as they are most relevant to the patients' subjective experiences and are commonly used to measure treatment effectiveness in clinical studies involving new investigational products for rhinitis treatment in humans [7,8]. Peak nasal inspiratory flow (PNIF) was used as it is comparable to but easier to perform than rhinomanometry [9] and judged more appropriate as patients made measurements at home. The correlation between nasal scores from clinical examination and degree of stuffiness has been described as weak [10] and therefore initial scoring of patients' nasal cavities was not performed. In the study patients were randomized to active or placebo treatment. As the actively treated patients would have recognized a later treatment without vibrations, a cross-over study design would have been unsuitable.

Low frequency vibration stimulation is, to the authors' knowledge, a novel treatment as no publications exist. Experience from this or similar mucosal and nasal cavity treatments is therefore not available [1,3].

Material and methods

This was a single-center, randomized (1:1), blinded, parallel-design study conducted at the ENT Clinic, Karolinska Institute, during February to July 2008. Patients with nasal stuffiness were self-selected for screening by responding to an advertisement and initial patient interviews were conducted by telephone. Patients, aged 18–62 years, otherwise healthy and without known allergy, with persistent symptoms of rhinitis (NAR), mainly blocked nose, without use of vasoconstrictor and daily symptoms of stuffiness (at least 3 months), or with an overuse (daily for previous 3 months) of vasoconstrictor (RM) were recruited. RM patients were permitted to use vasoconstrictors until visit 1, as discontinuation was not possible due to their addictive nature. NAR patients had to refrain from all rhinitis medication during a 2 week washout (before visit 1). Exclusion criteria were: nasal surgery, septum deviation, nasal polyps, known allergies, medication other than antihistamine and/or nasal steroids, and pregnancy.

A 2-week follow-up period was selected as this is a significantly longer treatment interval than that of steroid medication (often administered daily) and KOS could in future possibly be self-administered at home. Detailed power analysis was not performed as little was known about the potential clinical effects.

At visit 1 (day 0) patients met the study physician, were further informed regarding the study, and informed consent was collected. Patients were interviewed, clinically examined including the nasal cavity, and underwent standard allergy testing (Soluprick, ALK, Denmark). Compliance with inclusion and exclusion criteria was confirmed and patients were classified as belonging to either the NAR or the RM diagnosis groups.

Patients received a diary with symptom questions and equipment to measure PNIF (inspiratory flow meter and medium face mask; Clement Clarke Intl Ltd, Harlow, UK). On day 0 (morning), before the patients received treatment, the study physician demonstrated how to measure PNIF (record highest of three measurements, morning and evening, for 14 days), and instructed patients as to how to complete the diary questionnaires. The symptom questions regarding stuffiness, itching, and secretion had four grades (0, no; 1, light; 2, moderate; 3, severe) and were summed to a diary symptom score (DSS), ranging from 0 to 9. Patients' medication usage (type and amount), completed symptom questions, and an initial pretreatment PNIF measurement were recorded in the patient diary.

Patients within each treatment group were randomized (stratified for diagnosis: NAR or RM) to active or placebo treatment by the study nurse (not blinded to study treatment) who also performed the treatment. Patients received the first and only treatment on day 0. The treatment device was constructed by the investigator himself (Figure 1).

The treatment parameters were chosen so that treatment would be similar to natural turbulent oscillations and also not forceful or energetic enough to be potentially harmful. Before treatment (active or placebo), a paraffin-lubricated protective cover was applied over the device part to be inserted. The device was inserted into the nasal cavity and inflated to 50 mbar (0.05 atm) and treatment started. Active treatment, KOS, consisted of mechanical vibrations created using regular pressure oscillations (increases and decreases) at a frequency of 50 Hz. Placebo treatment consisted of a device maintaining stable pressure of 50 mbar. No oscillations were applied in the placebo treatment as any clinical effects of any such vibrations would be unknown. Treatment duration was 7 min in each nasal cavity.

At visit 2 (day 14), the study physician interviewed the patients. Patients who had experienced symptoms of upper airway infection were withdrawn from the study.

Patients completed the end of study questionnaire regarding their nasal symptoms, stuffiness on a scale 0–3 as previously described, and presence (1) or absence (0) of itching and secretion. The questionnaires were completed for nasal symptoms on day 14 and retrospectively for 1 week pretreatment, and days 1, 4, and 7 post-treatment. Answers were summed to a Rhinitis Questionnaire Symptom Score (RQSS), with range 0–5 for each time point.

Figure 1. Treatment apparatus.

The study design was approved by the Regional Ethics Committee in Stockholm (Box 289, SE- 171 77 Stockholm). Figure 2 shows a flow diagram of the study procedure.

Statistical methods

As pretreatment DSS and PNIF were measured at the clinic by the study physician and all post-treatment measurements were performed by the patient at home, pretreatment and post-treatment measurements were considered to be non-comparable, and results are presented for absolute values only. RQSS treatment assessments were performed at the clinic (day 14), therefore both absolute values and changes from before treatment (1 week pretreatment) to each of the time points, days 1, 2, 4, 7, and 14 are presented. Absolute values and differences were evaluated by the Wilcoxon signed rank test stratified for diagnosis (randomization strata: NAR, RM). Absolute PNIF values were evaluated using stratified analysis of variance (ANOVA) and PNIF. As stuffiness is most often the main problem for NAR and RM patients, results for overall RQSS and RQSS item 'stuffiness' are presented.

Results

Eighty-six patients were randomized. Eighty-four patients were treated (50 with NAR, 34 with RM). Six patients (four with RM, two with NAR) reported symptoms of upper airway infection and were excluded. Seven patients comprising three with NAR (two active treatment, one placebo) and four with RM (two active treatment, two placebo) were excluded from analysis due to non-compliance (Figure 2).

Seventy-one patients (35 active treatment, 36 placebo) were included in the analyses. Average age was around 40 years in both groups, 46% and 58% were females in the active treatment and placebo groups, respectively (Table I). At baseline (diary baseline = morning of day 0, end of study questionnaire baseline = assessment 1 week pretreatment), there were no statistically significant differences in median symptom scores (DSS and RQSS), or average PNIF, between treatment groups (Table I).

The results in the study would not have been materially different if excluded patients had been included.

Rhinitis questionnaire symptom scores

RQSS and RQSS item stuffiness were significantly higher in the placebo group compared with the active treatment group for day 1 ($p < 0.0001$ for both), day 2 ($p < 0.0001$ and $p = 0.0003$), day 4 ($p = 0.0088$ and $p = 0.0110$), and day 7 ($p = 0.0088$ and $p = 0.0110$). Median RQSS decreased in both treatment groups from the assessment 1 week pretreatment to assessments made post-treatment (all assessments made retrospectively on day 14) (Figure 3). Changes are significant at all post-treatment assessments ($p < 0.0001$) for the active treatment group, but not for the placebo group ($0.05 < p < 0.10$). The decrease in RQSS was significantly larger in the active treatment group compared with the placebo group ($p < 0.001$ for days 1, 2, 4, and 7 and $p < 0.01$ for day 14). For RQSS item stuffiness, there was a decrease in both treatment groups (Figure 4). Changes are significant at all post-treatment assessments ($p < 0.0001$) for the active treatment group, and at day 1 for the placebo group ($p = 0.0391$, $p = 0.0625$ all other assessment). Decrease in RQSS item stuffiness was significantly larger in the active treatment group compared with the placebo group ($p < 0.001$ for days 1, 2, 4, and 7 and $p = 0.0274$ for day 14). The median RQSS in the NAR and RM subgroups are presented in Figures 5 and 6. Note that, after 1 day: in the RM group, 85% of those receiving active treatment had a lower RQSS of at least one score unit (scale 0–5), vs 15% for placebo. For NAR, the corresponding figures were 82% and 22%, respectively. For RQSS item stuffiness (scale 0–3), active/placebo was 85%/15% for RM and 68%/22% for NAR. After 7 days: RQSS active/placebo for RM was 69%/15% (69%/15% for RQSS item stuffiness) and for NAR 50%/13% (41%/13% stuffiness). After 14 days: RQSS active/placebo for RM 54%/15% (54%/15% stuffiness) and for NAR 45%/13% (32%/13% stuffiness). The measured improvements could perhaps or even likely be of clinical importance.

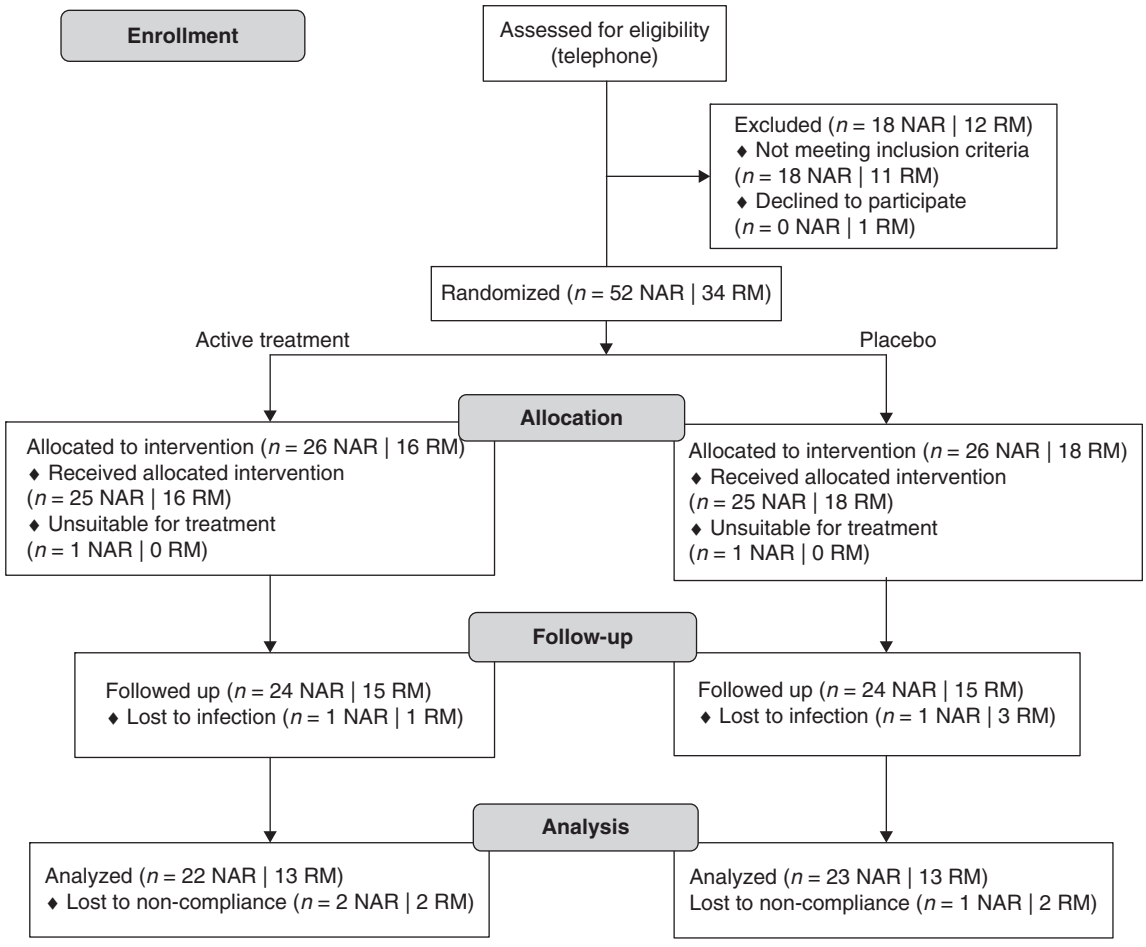

Figure 2. CONSORT flow diagram.

Diary symptom scores

In both the active treatment and placebo groups, median DSS varied between 2 and 3 but with no strong apparent pattern. The difference was significant on one occasion, day 1 morning, medians 2 and 3 in active treatment and placebo groups, respectively ($p = 0.0311$).

Peak nasal inspiratory flow

Average PNIF was higher in the placebo group compared with the active treatment group throughout the study period, and appeared generally stable throughout the period (significant day 0 evening, $p = 0.0485$; day 4 morning, $p = 0.0337$; day 5 evening, $p = 0.0474$).

Adverse events

During active treatment many patients sneezed and experienced repeated itchiness in and around the cartilaginous part of the nose. Many patients reported reduced sensitivity in the upper lip during treatment, which normalized a few minutes post-treatment. The study physician judged these events as mild. The majority of patients reported more stuffiness in the nose for several hours post-treatment.

Discussion

Data from this study indicate that KOS of the nasal mucosa with low frequency mechanical vibrations may have an impact on the symptoms of persistent rhinitis. RQSS and RQSS item stuffiness showed statistically significantly better symptom relief, both in absolute values and change from pretreatment, in the active treatment group compared with the placebo group. Relief was most notable the first week post-treatment but the symptom, as reflected by RQSS, remained statistically significantly reduced 14 days post-treatment in the active treatment group.

DSS and self-measured PNIF showed no significant effects, in accordance with other studies [11]. Overall, the results from DSS and PNIF did not

Table I. Background characteristics.

Characteristic	Statistics	Active treatment	Placebo	Total
Age (years)	No. of obs	35	36	71
	Mean (SD)	39.9 (11.4)	39.6 (10.9)	39.8 (11.1)
	Min, max	20, 59	22, 62	20, 62
Female	*n* (%)	16 (45.7%)	21 (58.3%)	37 (52.1%)
PNIF (L/min) [b]	No. of obs	32	36	68
	Mean (SD)	110.8 (30.9)	118.8 (32.9)	115.0 (32.0)
	Min, max	55, 160	40, 180	40, 180
	p value [a]			$p = 0.3047$
DSS [b]	No. of obs	33	36	69
	Median	2.0	3.0	3.0
	Min, max	1, 5	0, 9	0, 9
	p value [c]			$n = 69$, $p = 0.2321$
DSS [b] item stuffiness	No. of obs	33	36	69
	Median	2.0	2.0	2.0
	Min, max	0, 3	0, 3	0, 3
	p value [c]			$n = 69$, $p = 0.8226$
RQSS [d]	No. of obs.	35	36	71
	Median	3.0	3.0	3.0
	Min, max	1, 4	1, 5	1, 5
	p value value [c]			$n = 71$, $p = 0.1062$
RQSS [d] item stuffiness	No. of obs	35	36	71
	Median	2.0	2.0	2.0
	Min, max	1, 3	1, 3	1, 3
	p value [c]			$n = 71$, $p = 0.7991$

[a] Statistical testing of difference between treatment groups using ANOVA stratified for diagnosis (NAR, RM). [b] Day 0, morning. [c] Statistical testing of difference between treatment groups using Wilcoxon signed rank test stratified for diagnosis (NAR, RM). [d] Assessment for the week before the day 0 visit. NAR, non-allergic perennial rhinitis; RM, rhinitis medicamentosa.

indicate any differences between the groups, only few and marginally significant *p* values (between 0.05 and 0.01), which given the large number of statistical tests conducted may be due to multiplicity of testing. An analysis of change from pretreatment gave similar results. Symptoms scored in patient diaries at home did not seem to change, while the retrospectively reported symptoms (end of study RQSS) did. Diary data are known to be problematic in rhinitis studies. End of study questionnaires allow patients to reflect and compare pre- and post-treatment symptoms and may be more reliable.

In clinical studies a washout period before treatment and questionnaires grading both subjective symptoms and different objective measures of nasal flow are often recommended pre- and post-treatment. As patients with RM, in contrast to those with NAR, are addicted to vasoconstrictors they were considered unable to stop the use before treatment.

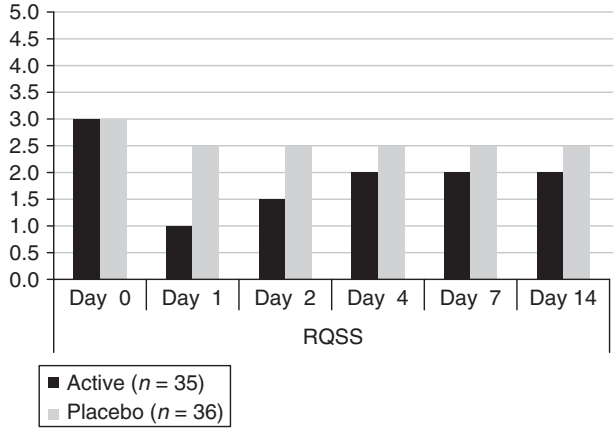

Figure 3. Median Rhinitis Questionnaire Symptom Score (RQSS), all patients (NAR and RM), score 0–5. NAR, non-allergic perennial rhinitis; RM, rhinitis medicamentosa.

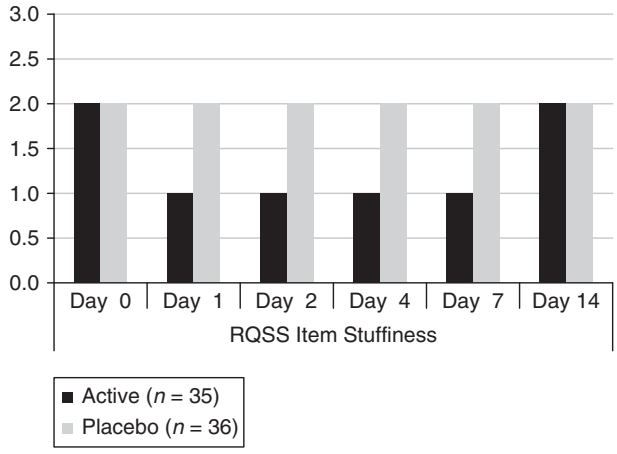

Figure 4. Median Rhinitis Questionnaire Symptom Score (RQSS) sub-item stuffiness, all patients (NAR and RM), score 0–3. NAR, non-allergic perennial rhinitis; RM, rhinitis medicamentosa.

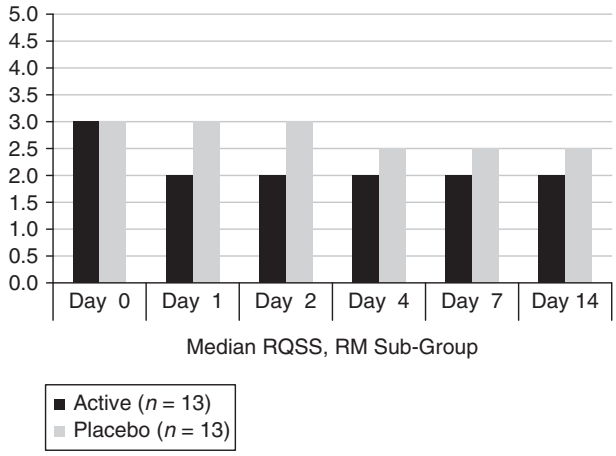

Figure 6. Median Rhinitis Questionnaire Symptom Score (RQSS), RM patients only, score 0–5. RM, rhinitis medicamentosa.

Patients in this study were classified as belonging to either NAR or RM at visit 1 (day 0), and the symptoms questionnaires were completed and PNIF measured only once at visit 1 (day 0), immediately before the administration of study treatment. Pre- and post-treatment DSS and PNIF were not considered comparable as they were measured under different circumstances. In addition, the visit to the clinic may have been associated with some stress that may have affected patients' experiences of symptoms. In the present study PNIF included very low (30–50) and very high (250–300) values. The PNIF measuring method has been shown to be highly effort-dependent and needs standardized techniques [12]. PNIF scores are only valid for maximum inspiration and not necessarily for normal breathing through the nose. As PNIF measures maximum inspiration it is not necessarily correlated to the patient's subjective sensation of blockage. Correlation between measurements and questionnaires range from positive to absent [10]. Some studies indicate that PNIF scores are highly reproducible and closely related to signs of rhinitis [13], others have reported that PNIF value measurements correlate poorly with rhinitis symptoms [8]. In the present study patients received daily questionnaires but it is unknown if patients completed them, and the PNIFs, daily. For diary data, it is reported that, in congestion evaluation, history is generally useful in determining the cause of congestion but weak in determining the success of treatment [10]. The follow-up period was limited to 14 days in this first controlled study, as a longer follow-up period could make patients' recall of symptoms pre- and post-treatment less reliable. The adverse events were few and mild. Some minor discomfort was experienced during active treatment but this disappeared shortly after treatment completion. Few patients reported airway infections, suggesting that study treatment did not facilitate the development of infections.

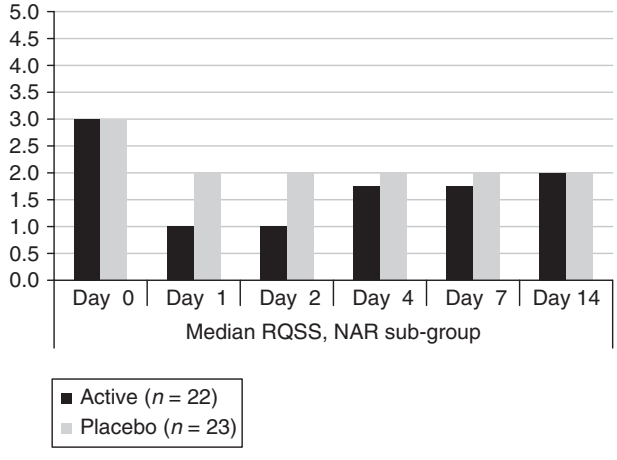

Figure 5. Median Rhinitis Questionnaire Symptom Score (RQSS), NAR patients only, score 0–5. NAR, non-allergic perennial rhinitis.

The choice of placebo can be discussed. It is known from the investigator's clinical practice that applied pressure alone does not relieve nasal stuffiness. Patients with nasal bleeding, treated with nasal cavity package for several hours to days, do not typically describe sustained decreased sensation of stuffiness. The placebo treatment applied stable pressure but no vibrations, which was not considered to have a sustained impact on the degree of stuffiness.

The mechanisms behind the obtained results have yet to be identified. It is possible that the mechanisms involved in relief of symptoms are not only release of transmitter substances such as neuropeptides, as the effect from active treatment lasts from days to weeks.

This long-term treatment effect may be explained by the active stimulation of sensory nerves and, directly

or indirectly, of the autonomic nervous system in the nasal cavity and plausibly the sympathetic part of the autonomic nervous system. It has been reported that patients with allergic rhinitis have a dysfunction in the autonomic nervous system, specifically a sympathetic hypofunction [14]. Other mechanisms of action could therefore be a balance change in each of, or between the two parts of the autonomic nervous system, sympathetic and parasympathetic nerves or in the nerve signal transmission itself [14–19].

In addition, local allergic rhinitis, detectable in the nose but not in the skin tests performed in the present study, may have impacted symptoms as patients sneezed and experienced nose itchiness during the stimulation.

Although these initial results are encouraging, further studies are required to understand the impact of the treatment and optimize it. Symptom questionnaires and longer pre/post-PNIF measurements would be useful in future investigations. Saccharine tests, cilia activity studies, were not performed but would be of interest as well as further studies of the association of non-allergic rhinitis with smoking and lower airway disease [20].

Conclusion

After one nasal mucosa treatment with KOS (low frequency mechanical vibrations), patients with NAR and RM had a significantly larger reduction of self-reported nasal symptoms, both overall (RQSS) and specifically of stuffiness, compared with placebo-treated patients. The effect was most pronounced in the days immediately following treatment but was still present 14 days post-treatment by some measures. Treatment was easy to administer, well tolerated by the patient, and side effects were few and mild. Considering that existing treatments (steroids and vasoconstrictors) are not always successful and can be addictive, the active treatment in this study has the potential to offer a viable alternative for symptom relief. Further studies are required to elucidate the mechanism of action and for optimization of the treatment.

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Declaration of interest: Professor Jan-Erik Juto is indirectly a major shareholder in Chordate Medical AG, a company active in the development of products based on kinetic oscillation stimulation (KOS) treatment. The authors alone are responsible for the content and writing of the paper.

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