ORIGINAL RESEARCH

A Complex Homeopathic Preparation for the Symptomatic Treatment of Upper Respiratory Infections Associated With the Common Cold: An Observational Study

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Background: The use of complementary medicines is large and growing in both the United States and Europe.

Objective: To compare the effects of a complex homeopathic preparation (Engystol; Heel GmbH, Baden-Baden, Germany) with those of conventional therapies with antihistamines, antitussives, and nonsteroidal antiinflammatory drugs on upper respiratory symptoms of the common cold in a setting closely related to everyday clinical practice.

Design: Nonrandomized, observational study over a treatment period of maximally two weeks.

Setting: Eighty-five general and homeopathic practices in Germany.

Participants: Three hundred ninety-seven patients with upper respiratory symptoms of the common cold.

Interventions: Engystol-based therapy or common over-the-counter treatments for the common cold. Patients receiving this homeopathic treatment were allowed other short-term medications, but long-term use of analgesics, antibiotics, and antiinflammatory agents was not permitted. Patients were allowed nonpharmacological therapies such as vitamins, thermotherapies, and others.

Main outcome measures: The effects of treatment were evaluated on the variables fatigue, sensation of illness, chill/tremor, aching joints, overall severity of illness, sum of all clinical variables, temperature, and time to symptomatic improvement.

Results: Both treatment regimens provided significant symptomatic relief, and this homeopathic treatment was noninferior in a noninferiority analysis. Significantly more patients ($P < .05$) using Engystol-based therapy reported improvement within 3 days (77.1% vs 61.7% for the control group). No adverse events were reported in any of the treatment groups.

Conclusion: This homeopathic treatment may be a useful component of an integrated symptomatic therapy for the common cold in patients and practitioners choosing an integrative approach to medical care.

Key words: Complementary medicine, observational study, noninferiority, viral infections

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INTRODUCTION

The common cold is a prominent example of an ailment in which multiple therapeutic approaches are commonly used in both alternative and conventional medical practices. There is no universally accepted therapy for the common cold, and no licensed antivirals appear to be effective for this condition. Some strategies, such as prolonged prevention of community colds with interferon are associated with adverse effects and are not recommended.[1] Thus, most treatments are addressed toward symptomatic relief, and there is a substantial component of self-medication involved.

Alternative medications are frequently used for treatment of musculoskeletal symptoms, vertigo, or mild viral infections, such as the common colds. There are data from clinical investigations indicating that, for the symptomatic treatment of mild viral infections, a therapy based on a complex homeopathic remedy may be as effective as conventional therapies with antihistamines, antitussives, and nonsteroidal antiinflammatory drugs (NSAIDS).[2]

One antiviral agent widely used in alternative medical practice is Engystol (Heel GmbH, Baden-Baden, Germany), a complex homeopathic preparation based on two main active ingredients, *Vincetoxicum hirundinaria* (common name, swallowort) and sulphur, at high dilutions (10^{-6} to 10^{-30}). Both ingredients are listed in the *Homeopathic Pharmacopoeia of the United States*.[3] This homeopathic treatment is used for acute symptomatic therapy as well as for prophylactic treatment of infectious diseases. In recent years, studies have reported beneficial effects of Engystol in different settings, such as prophylaxis in patients with influenza and common cold,[4] and there are reports suggesting stimulation of phagocytic activity of granulocytes in vitro.[5] A recent assay (Enbergs H, *Immunol Invest.* 2006, in press) indicated that Engystol might increase the percentage of interferon-γ producing lymphocytes in vitro.

This pilot study attempts to assess the clinical benefits of this homeopathic treatment compared with conventional treatment

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strategies in a real-life scenario and provide information that would be useful to plan a larger scale randomized controlled clinical trial. The duration of this study was not more than two weeks per patient, which corresponds to the maximum duration of the illness that might be encountered in clinical practice.

In an attempt to capture as wide a range of patients and therapeutic strategies as possible, this study used a nonrandomized, observational approach and includes capturing data on the use of concurrent medications. A disadvantage associated with this choice of design is the possibility that patients groups would not be comparable for all variables at baseline, which confounds the analysis of the results. To attempt to address this confounder, propensity score analysis was applied to the data. Such methods have been used in other studies with alternative medicine, eg, in a recent comparison of the homeopathic therapy Cralonin with conventional medications in patients with mild heart failure.[6]

METHODS

This observational study was carried out in 85 practices in Germany from November 1, 2003, to February 29, 2004. Inclusion criteria were symptoms of upper respiratory infections associated with the common cold before entering the study. Patients were excluded who were currently receiving symptomatic treatment for the common cold; patients with secondary bacterial infections of the upper respiratory tract on antibiotic therapy; patients with asthma, allergies, or chronic infections; and patients recently treated with similar therapies to those in the study.

Each center enrolled up to five patients into the study. Patients received Engystol-based therapy or common over-the-counter (OTC) treatments (antipyretic/analgesic/antiinflammatory) for the common cold. The choice of treatment was a joint decision of the practitioner and the patient. Engystol was given as tablets (active constituents: *Vincetoxicum hirundinaria* D6, D10, D30; sulphur D4, D10). To reflect everyday treatment practices, in both groups, the doses were not stipulated in the protocol but were decided for each individual patient for a maximum of two weeks. No limit was set to the number of different therapies in the control group. In the homeopathic treatment group, patients were allowed other short-term medications, but the long-term use of analgesics, antibiotics, and antiinflammatory agents was not permitted.

All patients were informed about the background and purpose of the study, which was conducted in full compliance with the principles of the Declaration of Helsinki and with the German recommendations for the planning, execution, and evaluation of observational studies (Bundesanzeiger Federal Gazette No. 299 of December 04, 1998).

All variables were selected to reflect patients' experiences of illness. Treatment effects were evaluated on the following variables: fatigue, sensation of illness, chill/tremor, temperature, aching joints, overall severity of illness, and the sum of all clinical variables. For the variables fatigue, sensation of illness, chill/tremor, aching joints, and overall severity of illness, severity was assessed on a scale from zero to three, where zero was asymptomatic; one, mild symptoms; two, moderate; and three, severe symptoms. Temperature was measured in degrees Celsius. In patients with diagnosis of rhinitis, pharyngitis, laryngitis, or bronchitis, changes in symptoms related to these diagnoses were also monitored. Rhinitis was assessed on sneezing, burning, or tickling sensations; nasal congestion; and reduced sensation of smell and nasal speech. Pharyngitis was evaluated as throat burns, pain with swallowing, and redness of mucous membranes. The laryngitis variables were loss of voice, hoarseness, cough, and soreness of throat. Finally, bronchitis was evaluated on cough, hoarseness, productive cough, and chest pain.

Tolerability was assessed through the monitoring of adverse events. Furthermore, the practitioner as well as the patients did an assessment of overall tolerability during the course of the study. The subjective tolerability experience was graded on a four-term scale: 0, excellent (no adverse reactions); 1, good (occasional adverse reactions); 2, moderate (frequent adverse reactions), and 3, poor (adverse reactions associated with every administration of study medication).

Statistical comparisons were conducted with ANOVA and Fischer's exact test as appropriate. To adjust for patients groups not being statistically comparable for certain variables at baseline, propensity-score analysis was carried out as previously described.[6] Patients were stratified into quintiles according to propensity score based on all baseline variables. The two treatment strategies were analyzed for noninferiority of Engystol-based therapy compared with conventionally based therapy. The noninferiority analysis compared the lower border of the 95% confidence interval between the differences in change between Engystol-based and conventionally based therapies. The noninferiority limits were set to 0.2 units for all symptomatic scores, 0.2°C for temperature, and 0.4 scoring units for the differences between the summary score of all variables.

RESULTS

A total of 397 patients were available for analysis, 175 in the homeopathic treatment group and 222 in the control group. Baseline characteristics are given in Table 1. The patients groups were generally well-balanced at baseline. There was a slightly higher number of women (58.3%) in the homeopathic treatment group than in the control group (52.7%), and patients in this group were somewhat shorter than those in the control group, but the differences were not statistically significant. The treatment groups differed significantly on four characteristics ($P < .05$ for the difference): weight, incidence of tracheitis and acute bronchitis, and fatigue score. Patients receiving the homeopathic remedy tended to be lighter and have lower incidences of tracheitis and acute bronchitis than the control patients, but they had slightly higher scores on fatigue than the control patients. Propensity score stratification adequately compensated for these differences, which were reduced beyond the threshold of significance ($P < .05$).

The homeopathic treatment group received treatment in the form of tablets, commonly given three times daily (69.6%). This dosage was not fixed, and increased dosing was used intermittently by 73.7% of patients. The most commonly used other study treatments in the control group were paracetamol (42%), aspirin (16%), metamizol (18%), and ibuprofen (12%).

Table 1. Baseline Characteristics

Variable	Engystol (n = 175)	Control (n = 222)
Mean age years (±SD)	35.1 (±18.7)	38.6 (±16.9)
Female sex, n (%)	102 (58.3)	117 (52.7)
Mean weight, kg (SD)*	65.7 (±19.5)	69.7 (±17.1)
Mean height, cm (SD)	166.2 (±20.1)	169.0 (±18.5)
Nonsmokers, n (%)	135 (77.1)	167 (75.2)
Acute bronchitis, n (%)*	69 (39.4)	113 (50.9)
Tracheitis n (%)*	39 (22.3)	70 (31.5)
Baseline values (mean score ±SD)		
Fatigue*	2.2 (±0.7)	2.0 (±0.7)
Sensation of illness	2.2 (±0.7)	2.1 (±0.7)
Chill/tremor	1.5 (±0.9)	1.4 (±0.9)
Aching joints	1.9 (±0.9)	1.7 (±0.9)
Overall severity of illness	2.3 (±0.6)	2.3 (±0.6)
Temperature (degrees Celsius ±SD)	38.1 (±0.9)	38.0 (±0.9)
Subgroups (summary scores ±SD)		
Rhinitis	8.3 (±2.8)	7.9 (±3.2)
Pharyngitis	6.1 (±1.9)	5.6 (±1.7)
Laryngitis	6.6 (±2.7)	6.8 (±2.1)
Bronchitis	5.5 (±2.5)	5.5 (±2.2)

Asterisks indicate differences between treatment groups ($P < .05$) before adjustment for propensity score.

The protocol allowed for the use of additional therapies not included among the defined study medications, and both groups made use of such remedies. In the homeopathic treatment group, menthol- or camomile-based inhalations were used by 57.7% of patients, vitamins by 37.7%, sympathomimetic decongestants by 27.4%, and antipyretics/analgesics by 23.4% of patients. The most common nonstudy therapies in the control group were cough remedies (antitussives/expectorants) (59.0%), menthol- or camomile-based inhalations (53.5%), vitamins (34.7%), and decongestants (24.3%).

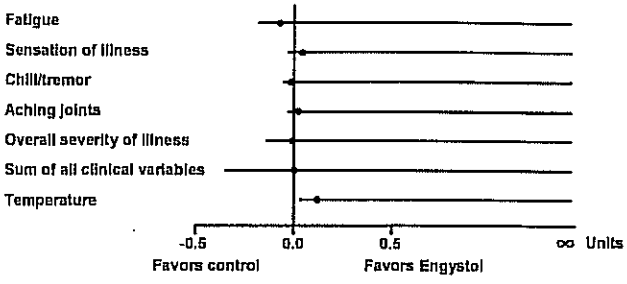

Figure 1. Point estimate and left border of the 95% confidence interval for the difference between the Engystol and control groups for the main variables.

Symptoms of common cold were reduced in both treatment groups during the observation period of maximally two weeks. For most variables, there were no statistically significant differences between the two groups. Fatigue was reduced by 1.8 ± 0.7 units (±SD) by Engystol-based therapy and by 1.7 ± 0.8 units by control therapies. For the variable sensation of illness, the reductions were 2.1 ± 0.7 and 1.9 ± 0.7 units in the homeopathic treatment and control groups, respectively. Chill/tremor scores were reduced by 1.5 ± 0.9 units in the Engystol-based therapy and by 1.3 ± 0.9 units in the control therapies group. Aching joints score was 1.8 ± 0.9 units lower at the end of therapy than at baseline with homeopathic treatment and 1.7 ± 0.9 units lower with antipyretic/analgesic/antiinflammatory treatments. The overall severity of illness score was reduced by 1.8 ± 0.7 units in the homeopathic treatment group and by 1.8 ± 0.8 units in the control group.

For the sum of all clinical variables, the reductions were 7.9 ± 2.6 and 7.2 ± 2.6 units in the Engystol and the control groups, respectively. The temperature was lowered by 1.5°C ± 0.9°C with homeopathic treatment and by 1.3°C ± 0.9°C with the control therapies.

The results of the noninferiority analysis are summarized in Figure 1 and Table 2. For the variables overall severity of illness, aching joints, and temperature, the point estimate for the differences in score change from baseline to end of study between homeopathic-based therapies and conventionally based therapies fell on the right-hand side of unity, indicating a trend to-

Table 2. Change From Baseline to Final Visit in Main Variables

Variable	Left Border of 95% Confidence Interval (score units)	Noninferiority Limit (score units)	Noninferiority Demonstrated
Fatigue	−0.19	−0.2	Yes
Sensation of illness	−0.04	−0.2	Yes
Chill/tremor	−0.06	−0.2	Yes
Aching joints	−0.03	−0.2	Yes
Overall severity of illness	−0.13	−0.2	Yes
Sum of all clinical variables	−0.36	−0.4	Yes
Temperature	0.03	−0.2	Yes

Table 3. Change From Baseline to Final Visit in Summary of Symptom Scores for Subgroups With Different Specific Diagnoses

Subgroup	Engystol (n)	Control (n)	Mean Change (95% CI), Engystol	Mean Change (95% CI), Control	Difference Control-Engystol (95% CI)
Rhinitis	124	149	−7.3 (−7.8 to −6.8)	−7.0 (−7.6 to −6.5)	−0.2 (−0.8–0.4)
Pharyngitis	117	140	−5.6 (−6.0 to −5.3)	−5.0 (−5.3 to −4.7)	0.4 (−0.0–0.8)
Laryngitis	46	56	−5.8 (−6.5 to −5.1)	−6.0 (−6.5 to −5.4)	−0.3 (−1.0–0.4)
Bronchitis	82	136	−4.6 (−5.1 to −4.0)	−4.4 (−4.8 to −4.0)	0.2 (−0.4–0.8)

ward favoring Engystol treatment. The fatigue score tended toward favoring conventional therapies, whereas, for the other variables, there were no trends toward differences between the groups. The analysis supported the noninferiority of Engystol-based therapy compared with conventional therapy for these variables (Table 2).

The subgroup analyses in the groups with rhinitis, pharyngitis, laryngitis, or bronchitis showed trends toward greater effects with the conventional treatment regimen compared with homeopathic treatment, but the lower border of the 95% confidence interval supported the noninferiority of Engystol (Table 3; note that the numbers given are changes in summary scores of all specific variables for each subgroup). Improvements from baseline were observed in both treatment groups during the course of the study.

The time to first global symptomatic improvement was between one and three days in the majority of patients in both treatment groups (Figure 2). Patients in the Engystol group generally reported signs of symptomatic improvement at earlier time points than did patients in the control group. Three fourths (77.1%) of Engystol patients reported improvement within three days, compared with 61.7% in the control group. This difference was statistically significant at a level of $P < .05$.

Both therapeutic strategies achieved high patient satisfaction, with 97.7% of patients reporting themselves to be "very satisfied" (54.9% and 52.7% in the Engystol and control groups, respectively) or "satisfied" (42.9% and 45.5% in the homeopathic treatment and control groups, respectively). There were no significant differences in satisfaction scores between the treatment groups.

Tolerability was very good with both treatment regimens. No adverse events were reported in any of the treatment groups. More patients (89.2%) reported "excellent" overall tolerability with homeopathic treatment than with control therapies (81.2%; Figure 3A). For unadjusted data, this difference was statistically significant ($P = .01$); however, when patients were adjusted for propensity score, the differences in tolerability no longer reached significance.

The good tolerability scores were further reflected in patient compliance with both treatment strategies (Figure 3B). Compliance was rated as "excellent" for 61.1% and 60.8% of patients in the homeopathic treatment and control groups, respectively. A score of "good" was given for 37.7% of patients in the homeopathic treatment group and 37.4% of patients in the control group. The differences in compliance scores were not statistically significant.

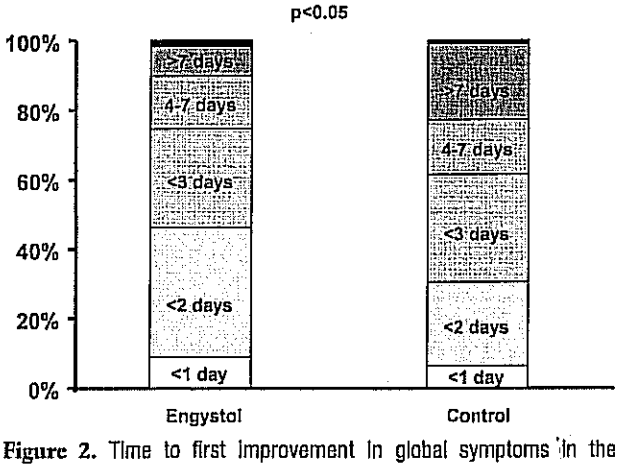

Figure 2. Time to first improvement in global symptoms in the Engystol group (left-hand bar) and the control group (right-hand bar), respectively. The differences between the groups were significant at a level of $P < .05$.

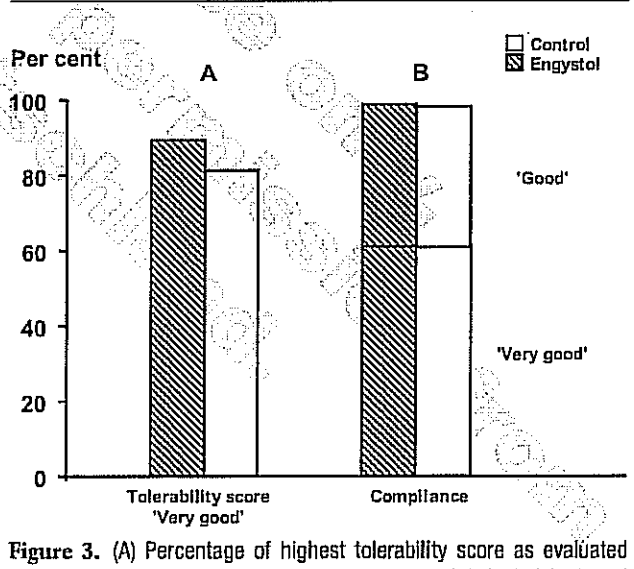

Figure 3. (A) Percentage of highest tolerability score as evaluated jointly by physician and patient for the Engystol (stippled bar) and control groups, respectively. (B) Percentages of the two highest scores of physician-assessed compliance for the two treatment groups. The differences between the treatments were not statistically significant.

DISCUSSION

The results of this exploratory nonrandomized, observational study indicate that, for treatment of the common cold, a therapy based on the complex homeopathic preparation Engystol may be noninferior to therapies based on conventional medications for this condition. This conclusion was reached from an analysis of the effects on five illness-related symptoms, on the summary score of all variables, and on overall assessment of illness severity. The strengths and weakness of the study are associated with its nonrandomized, observational design, and the fact that the diagnosis studied is a self-limiting diagnosis. The design was chosen to approach as closely as possible to clinical practice, which may differ substantially between complementary and conventional therapies. A randomized design may have missed out on many of the wide range of patients who are taking complementary medications.[7] The nonrandomized approach has the potential drawback that patients groups are not likely to be comparable for all variables. In the present case, the treatment groups differed at baseline for weight, incidence of tracheitis and acute bronchitis, and fatigue score. However, there are standard statistical procedures available potentially to deal with such differences. The method chosen, propensity score, describes the conditional probability of receiving treatment, given the observed covariates. By applying this balancing score to the data, it was possible to reduce but not eliminate bias.[8]

Another limitation associated with this study is the variability in dosing and the fact that a number of nonstudy therapies were used in both treatment groups in addition to the specified study regimens. Close to one in four patients in the homeopathic treatment group took antipyretics/analgesics for acute symptomatic relief, which likely had a certain confounding effect on the analysis. However, long-term use of antipyretics/analgesics was not allowed in the homeopathic treatment group, and it is less likely that the brief short-term use of such agents in 25% of the population was responsible for the effects seen in the overall homeopathic treatment group.

This treatment pattern in the homeopathic treatment group is interesting because it indicates a pragmatic approach to therapy in many patients opting for complementary therapy. This pragmatism was evident, not only in the homeopathic treatment group, but also in the control group, in which a large number of patients (>35%) took supplementary vitamins. Particularly in mild illnesses such as the common cold, there is no fixed border between conventional and complementary medicine, and there is a large component of self-medication. A number of remedies are available to achieve symptomatic relief from cold symptoms,[9,10] and the willingness of study participants in both treatment groups to use such options shows that public attitudes toward medication crosses the borders between conventional and alternative medicines for mild illnesses.

Another possible weakness is that our scoring methods have not yet been validated in independent studies. Furthermore, the definitions of borders of any noninferiority analysis will be open to debate, as recently seen in a randomized trial in 15,000 patients receiving two different treatments postmyocardial infarction.[11] The noninferiority borders in our study were set quite tight, at 10% to 15% of the respective baseline values, and the differences between the treatment groups were small, which supports our conclusions.

It might be argued that acute mild viral infections such as the common cold normally resolve spontaneously over a course of several weeks.[9,10] Although the natural course of infection may push the outcomes at the end of the observational period toward noninferiority, the high satisfaction and compliance scores with both treatments indicate that patients perceived real benefits from treatment in both groups, even if they were potentially not related directly to the therapy administered. In a study attempting to capture real-life treatment situations, the patients' perspective is an important factor in evaluating the effectiveness and usefulness of therapies. It is worth pointing out that, in the context of patients' satisfaction, the differences in time to first symptomatic improvement may be relevant. The time to first symptomatic improvement was shorter with homeopathic treatment than with the control therapies.

In a study involving a homeopathic preparation, the question inevitably arises as to the potential mechanisms of action behind the effects. A placebo effect should not be ruled out, although it appears unlikely for several reasons. Such an effect would have to have been greater in the homeopathic treatment group than in the control group, or, alternatively, the conventionally treated patients would have experienced a paradoxical negative effect from treatment. This homeopathic treatment has a history of use as a prophylactic treatment of respiratory infections[12] and as an ancillary treatment of viral infections in infants.[4] In vitro studies have shown stimulation by Engystol of the immune system in terms of phagocytic activity, granulocyte function, and improved humoral response.[13–15] It is currently unclear whether these effects are mediated by the immunostimulatory properties of Engystol or whether this particular complex homeopathic remedy by itself has a direct antiviral activity. A recent assay (Enbergs H, *Immunol Invest.* 2006, in press) has indicated that Engystol may increase the percentage of interferon-γ producing lymphocytes in vitro. The need for biochemical mechanistic data on this remedy as with most of homeopathic treament remains, in part, unmet.

Both treatments demonstrated good tolerability profiles; the trend toward the score "very good" in more patients in the Engystol group was not significant. Complementary medications in general are associated with low incidences of adverse effects (which may be one reason for their popularity). In more serious medical conditions, patients might be unwilling to comply with a trade-off between benefits and adverse effects. There are no known adverse effects reported for this complex homeopathic remedy,[16] and this study is consistent with the findings already on record for this medication. In summary, based on the limited results of this observational study, Engystol appears to be an acceptable component of an integrated symptomatic therapy for the common cold.[13-16]

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