Effectiveness of an Herbal Preparation Containing Echinacea, Propolis, and Vitamin C in Preventing Respiratory Tract Infections in Children

A Randomized, Double-blind, Placebo-Controlled, Multicenter Study

Herman A. Cohen, MD; Itzchak Varsano, MD; Ernesto Kahan, MD, MPH; E. Michael Sarrell, MD; Yosef Uziel, MD

Objective: To evaluate the effectiveness and safety of a preparation containing echinacea, propolis, and vitamin C in the prevention of respiratory tract infections in children during a 12-week winter period.

Design: Randomized, double-blind, placebo-controlled study.

Subjects: Four hundred thirty children, aged 1 to 5 years, were randomized to an herbal extract preparation (n=215) or a placebo elixir (n=215).

Intervention: Administration of an herbal preparation (Chizukit) containing 50 mg/mL of echinacea, 50 mg/mL of propolis, and 10 mg/mL of vitamin C, or placebo (5.0 mL and 7.5 mL twice daily for ages 1 to 3 years and 4 to 5 years, respectively) for 12 weeks.

Results: Significant mean±SD reductions of illnesses were seen in the Chizukit group in the number of illness episodes, 138 vs 308 (55% reduction); number of episodes per child, 0.9±1.1 vs 1.8±1.3 (50% reduction, \(P<.001\)); and number of days with fever per child, 2.1±2.9 vs 5.4±4.4 (62% reduction, \(P<.001\)). The total number of illness days and duration of individual episodes were also significantly lower in the Chizukit group. Adverse drug reactions were rare, mild, and transient.

Conclusion: A preventive effect of a product containing echinacea, propolis, and vitamin C on the incidence of respiratory tract infections was observed.

immune system. Ascorbic acid has been reported to increase the proliferative responses of T lymphocytes in vitro and to induce the production of interferon in cell culture. Vitamin C concentrations are up to 100 times greater in phagocytes and lymphocytes than in plasma, suggesting a physiological role in these immune system cells.

Despite the widespread use of echinacea and propolis, their efficacy remains controversial. Clinical results supporting their effectiveness in the treatment and prevention of upper respiratory tract infection have been published primarily in German and only from trials among adults. The objective of the present study was to investigate the effectiveness of a preparation containing echinacea extract, propolis, and vitamin C (Chizukit; Hadas Corp Ltd, Yokneam, Israel) in preventing upper respiratory tract infections in children.

METHODS

SUBJECTS

A randomized, double-blind, placebo-controlled design was used. The study was performed during the winter between November 1, 1999, and March 30, 2000. It took place at 10 primary care pediatric community clinics in Israel. The study sample consisted of 430 children aged 1 to 5 years, 215 each randomized to placebo elixir or active Chizukit groups. The sample size calculation was based on a previous study that showed a crude rate of 17.8% reports of flulike and acute respiratory symptoms during a winter period. Although that population (mean age, 28 years) was not restricted to children, other characteristics, such as membership in the Israeli Health Insurance System, seasonality, and 12 weeks’ observation, were similar to those among the population of the present study. Assumptions for the calculation were based on a 0.18 probability of colds in the placebo group, estimating that we had 90% power with α = .05 to detect a relative risk of 0.5.

Under these conditions, the minimum sample size for each group is 134 subjects. Adding 50% to accommodate probable dropouts, the sample size increased to 201. Although it is expected that a population of children in a clinical trial will report more events than the general population, reducing the sample size needs, we added an extra 10% (13.4 subjects) in case the reported rate in children was lower. Therefore, the final calculated sample size was 215 subjects for each trial group. Exclusion criteria were presence of acute upper respiratory tract infection or other infections within the 7 days before consideration for the study; cystic fibrosis; immunodeficiency syndrome (acquired or congenital), anatomic abnormalities of the respiratory tract (acquired or congenital), malabsorption, or use of immunostimulating or immunosuppressive drugs within 4 weeks before inclusion in the study. Eligible patients were randomly assigned to receive 12 weeks’ treatment with placebo elixir or active Chizukit, a preparation containing an extract of 50 mg/mL of echinacea (upper plant parts of E angustifolia and roots of E purpurea), 50 mg/mL of propolis, and 10 mg/mL of vitamin C. Chizukit is a standard combination widely used in Israel as an over-the-counter drug. Group allocation was done according to a computer-generated randomization list in blocks of 4. The medication or placebo was administered following the company recommendations, twice daily, in a dosage of 5.0 mL for children aged 1 to 3 years and 7.5 mL for children aged 4 to 5 years. If an episode of acute illness occurred during the study, the dosage was increased to 5.0 mL and 7.5 mL, respectively, 4 times daily during the episode only. The medication or placebo was packed in boxes containing 5 bottles of 250 mL each. The boxes and bottles were identical, and the Chizukit and placebo extracts were indistinguishable by appearance, color, or flavor. The Chizukit and the placebo were supplied directly by the manufacturer, and all randomization lots were stored in a sealed envelope at the pharmacy of the company, to be opened only in the event of an emergency.

At the outset of the study, the parents were given the first box of Chizukit or placebo and were instructed to administer it according to schedule. They also received a diary card to record any acute episodes of respiratory tract illness, specific symptoms (fever, runny nose, and nighttime and daytime cough, if more than usual), use of antipyretic or antibiotic agents, absence from day care or kindergarten, and physician office visits (other than those scheduled). Follow-up visits were conducted at 4, 8, and 12 weeks to hand out new medication, collect data on respiratory morbidity and adverse drug reaction, and monitor compliance. All other visits because of respiratory symptoms were considered unscheduled visits. The participants were asked to contact the study physicians in the event of symptoms of upper respiratory tract infection to confirm the existence of the acute episode of respiratory illness. The final registration of an illness episode was made only if such a confirmation was done. We define an adverse drug reaction as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, that predicts hazard from future administration and warrants prevention or specific treatment, alteration of the dosage regimen, or withdrawal of the product. In addition, a study coordinator weekly telephoned the parents to obtain information regarding the occurrence of acute respiratory episodes, symptoms, and use of additional prescribed medication (antipyretics, antibiotics, and decongestants). An episode of acute illness was defined as the appearance after at least 5 symptom-free days of 1 or more major signs together with at least 1 minor sign, as follows: major signs, fever greater than 38°C, acute otitis media, tonsillopharyngitis with severe redness or exudates, and auscultatory finding compatible with pneumonia; and minor signs, hoarseness or stridor, conjunctivitis, cough, and runny nose (significantly more than usual). The duration of an episode was measured from the onset of symptoms to the return to the baseline condition, based on parental assessment.

The local ethics committee of the Schneider Children’s Medical Center of Israel approved the study. All parents gave informed consent to participate before starting the study.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS for Windows, version 10.0 (SPSS Inc, Chicago, Ill). The differences between proportions test was used to determine the significance of differences in nominal variables (number [percentage] of children with ≥1 episodes in Table 1, and incidence of respiratory system infection in Table 2) between the groups, and a t test was used to compare the mean number of days with symptoms and means of the other variables. For the relevant variables, mean ± SD and 95% confidence intervals were calculated.
the Chizukit and placebo groups, respectively), lack of confidence in the treatment (4 subjects and 1 subject), and noncompliance without any explanation (24 subjects and 21 subjects). Because all of the differences between the Chizukit and placebo groups (rate of withdrawal and reasons for it) were not significant (P approaching 1.00 for all) and because all dropouts occurred during the first week of the study, we performed an efficacy study instead of an intention-to-treat analysis. The Figure shows the subject progress through the phases of the trial.

The primary outcome data are presented in Table 1. The number of children who experienced 1 or more respiratory tract illness episodes during the 12 weeks of the study, the total number of episodes, and the mean number of episodes per child were significantly lower in the Chizukit than the placebo group (by 43%, 55%, and 50%, respectively). The total number of illness days and duration of individual episodes were also significantly lower in the Chizukit than the placebo group (by 43%, 55%, and 50%, respectively). The total number of episodes per child was 1.6 ± 1.9 in the Chizukit group and 2.6 ± 4.2 in the placebo group (P < .001). The duration of individual episodes was 1.8 ± 1.3 days in the Chizukit group and 2.9 ± 1.6 days in the placebo group (P < .001). The number of days absent from school or kindergarten were significantly lower in the Chizukit group. Similar findings were noted according to parental report, was lower by 22%, 30%, and 36%, respectively, in the Chizukit group, but these differences did not reach statistical significance, except for nighttime cough (P = .03). The respiratory system diseases diagnosed during the study are summarized in Table 2. Upper respiratory tract infection was the most frequent, followed by acute otitis media. There were few cases of pneumonia and tonsillitis. The incidence of each of the diseases was significantly lower in the Chizukit group.

Adverse drug reactions were observed in 9 patients (5.6%) in the Chizukit group and 7 (4.2%) in the placebo group (P = .54). All were mild gastrointestinal and palatability symptoms that were transient and did not require discontinuation of treatment.

The results of the present study demonstrate, for the first time, that an herbal preparation containing an extract of echinacea, propolis, and vitamin C has a significant beneficial effect on the incidence and severity of respiratory tract infections in young children (as in adults). Recently, Mark et al.30 reviewed the use of echinacea in the pediatric population and described their trial evaluating the effect of echinacea in preventing recurrent otitis media.

Several studies30,31,32,33 have investigated the effectiveness of various preparations of echinacea extracts for the treatment and prevention of respiratory tract infection in adults. Barret et al.31 reviewed the evidence on orally administered echinacea extracts for acute upper respiratory tract infections and concluded that they may be beneficial for the early treatment of existing illness but not for prevention. The same conclusion was reached by Melchart4 and Gunning33 and their colleagues. However, Schoneberger,33 in an 8-week trial, noted a shorter duration of illness and a trend toward fewer study participants with infection, indicating a possible preven-
The present study demonstrates that an herbal extract preparation containing echinacea, propolis, and vitamin C may be beneficial for the prevention of respiratory tract infections in children. Advice regarding the use of herbal extracts, especially for children, is recommended.

Propolis has been shown to have anti-inflammatory and antiviral activity. Crisan et al reported a lower incidence of rhinopharyngeal infection and symptoms in a group of preschool children treated with a propolis preparation for 5 months. The authors suggest that the decrease in the local virus and bacterial carriage rate in the nasopharynx was attributable to the anti-inflammatory and decongestive properties of the product.

We do not believe that the low dose of vitamin C in the Chizukit preparation by itself plays a role in the prevention of respiratory tract illness. However, some additive effects to echinacea and propolis immunomodulation cannot be ruled out.

The safety data on echinacea are relatively strong. It also appears to be well tolerated, with a low frequency of adverse effects, such as unpleasant taste, nausea or vomiting, abdominal pain, and diarrhea. This was also observed in the present study. However, serious allergic or anaphylactic events have been reported in rare cases, so caution is advised for patients with a history of hypersensitivity to products from the daisy family (sunflower seeds and ragweed).

Melchart et al suggested that echinacea may be beneficial for individuals who already have an immune disorder but that it has little or no effect on a healthy immune system. The use of immunostimulants in the prevention of upper respiratory tract infection is controversial. Berber and Del-Rio-Navarro conducted a meta-analysis study and reported that immunostimulants can reduce the incidence of acute upper respiratory tract infection in children but cannot prevent all these infections. Therefore, they suggest that the use of immunostimulants for prevention must be limited to children with high susceptibility to these kinds of infections or to overexposed children attending day care centers, kindergartens, or elementary schools. We assume that the beneficial effect of the Chizukit preparation in this study was due to the immunomodulatory action of its components. The immunostimulating properties of echinacea may decline with continued use. Therefore, some authors suggest that preparations containing echinacea not be taken for longer than 8 to 12 consecutive weeks.

One limitation of the present study is the lack of appropriate quality control and standardization, because the active components of the preparations are not known. In addition, the safety of long-term prophylactic use was not tested.

The present study suggests that an herbal extract preparation containing echinacea, propolis, and vitamin C is beneficial for the prevention of respiratory tract infections in children. However, considering that this is the first trial conducted in young children, conclusions must be made with caution. Additional studies are needed in larger samples to confirm our findings and to rule out the potential adverse effects in general or specific populations at risk, such as allergic children or those receiving cotreatment or having different morbidities, before the preparation can be recommended for routine clinical use.

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REFERENCES

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27. Corresponding author: Herman A. Cohen, MD, Pediatric and Adolescent Ambulatory Community Clinic, Hashadrut 23, Petach Tikva 56000, Israel (e-mail: hermanc@post.tau.ac.il).
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