Echinacea purpurea for Prevention of Upper Respiratory Tract Infections in Children

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ABSTRACT

Objective: The aim of this study was to determine whether Echinacea purpurea given to children for the treatment of acute upper respiratory tract infection (URI) was effective in reducing the risk of subsequent URI.

Design: This was a secondary analysis of data from a randomized, double-blind, placebo-controlled trial of Echinacea for the treatment of URI in children.

Setting: The study was conducted as a joint project between the Puget Sound Pediatric Research Network (Seattle, WA) and Bastyr University (Kenmore, WA).

Participants: A total of 524 children ages 2 to 11 years were enrolled in the study.

Intervention: Children were monitored for URIs over a 4-month observation period during the fall/winters of 2000–2001 and 2001–2002. At entry the children were randomized to receive Echinacea or placebo to treat acute URIs during the observation period.

Main outcome measures: The occurrence of a second URI and the number of days between the end of the first URI and the start of the second URI was ascertained. Survival and Cox regression analyses were used to determine whether children who took Echinacea for their URIs were less likely to develop subsequent URIs.

Results: Among the 401 children with at least one URI treated with study medication, 69.2% of those receiving placebo developed a second URI versus 55.8% of those who received Echinacea. Use of Echinacea was associated with a 28% decreased risk of subsequent URI (p = 0.01, 95% confidence interval 8%–44% decreased risk).

Conclusions: Echinacea purpurea may be effective in reducing the occurrence of subsequent URIs in children. However this finding needs to be replicated in a URI prevention trial.

INTRODUCTION

Echinacea is one of the most commonly used medicinal plants in the western world and was the top-selling herb in the United States in 2002. Market statistics for 2000 indicate that $58.4 million was spent on Echinacea products in the United States at “mass market” outlets. Because this does not include sales from buying clubs, natural foods markets, health professionals, or the Internet, this figure is an underestimate.

The most common uses of Echinacea are for treatment or prevention of the common cold. Biologically, extracts of Echinacea have been shown to activate ex vivo human macrophage cells and polymorphonuclear cells by increas-
Echinacea may modulate immune function, decreasing the susceptibility to upper respiratory tract infections. A number of studies have been conducted to assess the efficacy of various Echinacea products to treat and prevent upper respiratory tract infections (URIs) in adults. However, these reviews did not include the results of a recent trial in which no efficacy of Echinacea in the treatment of URIs in young adults was demonstrated. Further larger-scale studies have been recommended. Of the published Echinacea prevention studies in adults, at least six included a placebo control group. The results of these prevention trials suggest a 12%–20% reduction in the subsequent occurrence of upper respiratory infections after Echinacea treatment. Unfortunately several of these trials have been underpowered to detect an effect of this magnitude.

Until recently no studies have examined the effect of Echinacea in children. The current research group conducted a large randomized, double-blind, placebo-controlled, treatment-efficacy trial in 524 children ages 2–11 years. It was found that a preparation of the reconstituted dried juice of the above-ground plant parts of Echinacea purpurea (Echinacea) did not shorten the duration or lessen the severity of URIs. The current study is a formal secondary analysis to determine whether taking Echinacea for the treatment of URI reduces the risk of a subsequent URI.

### MATERIALS AND METHODS

The study was conducted as a joint project between the Puget Sound Pediatric Research Network and Bastyr University. The methods of the study have been previously published. Briefly the study enrolled healthy children, 2–11 years old whose parents were available to observe them overnight and who read English. Children were not allowed to participate if they had a history of allergic rhinitis, asthma, lung disease, or autoimmune diseases; known allergy to Echinacea or sunflower species; or daily use of medications. Rolling enrollment of children into the study occurred between September and January in each of the 2 years 2000–2001 and 2001–2002. Children were randomized to receive either a non-alcohol Echinacea purpurea liquid (reconstituted dried pressed juice of the above-ground plant parts harvested at flowering) or a similar placebo liquid for acute URIs that occurred during the study period. The mass ratio of Echinacea purpurea (fresh plant) and the dried pressed juice obtained from it is 31.5–53.6 : 1, which is stored in a dried form and undergoes mild evaporation. The dried pressed juice is reconstituted with 100 g of the finished medicinal product containing 2.34 g of the dried pressed juice (23.4 mg/mL of the concentrated extract). The product used for the trial is formulation of preparation EC31J2, which is marketed as Echinacin® Saft (Madaus AG, Cologne, Germany). At the time the study was designed, the product used in this trial was the number-1–selling Echinacea extract in the world and was available in a non-alcohol form with dosing instructions for children. In addition the German Commission E monographs indicated that Echinacea purpurea herb was approved for supportive therapy for colds. Treatment of acute URIs was the aim of the initial study on which this secondary analysis is based.

Randomization was done in blocks of 10 in consecutively numbered sets of study medication. Children were followed for 4 months or a total of three URIs, whichever occurred first. A total of 524 participants were enrolled in the randomized controlled trial. For this report, data from children who received study medicine for at least one URI during the observation period were analyzed in an intent-to-treat manner.

Parents were instructed to call study staff at the first sign of URI symptoms. The study staff verbally verified that the child had at least two symptoms of a URI (cough, fever, nasal congestion, runny nose, sneezing) and reviewed dosing instructions with the parent (3/4 tsp [87.75 mg] twice a day for children 2–5 years, 1 tsp [117 mg] twice a day for children 6–11 years). Parents were instructed to give the study medicine until symptoms abated up to a maximum of 10 days and to record the severity of URI symptoms in a log book until they resolved up to a maximum of 21 days. Parents were asked to return completed log books to the research team at the end of the URI. Study investigators remained blinded to each child’s randomization status until the analysis.

For this analysis the primary outcomes were the incidence of a second URI and the number of days between the end of the first URI and the start of a subsequent URI. The end of the first URI was defined as the last day that any symptoms were recorded in the log book plus 7 days (the additional 7 days were included to ensure that any symptoms occurring in a participant were from a new URI and not merely symptoms lingering from the previous URI). Thus the second primary outcome could be determined only in participants whose symptom log books were received. The start of the subsequent URI was defined as the day that the parent telephoned study staff and a new URI was verified.

Survival analysis was used to determine whether the length of time between first and subsequent URIs was different among children in the Echinacea and placebo groups. The follow-up time for incidence of second URIs was not different between the participants taking Echinacea and placebo. Kaplan-Meier curves were generated to depict the time to onset of a subsequent URI in the two intervention groups, and median time between the end of the first URI and subsequent URI in the two groups was computed. The log-rank test was performed to determine whether there was a significant difference between the curves. For children
with only one URI the number of days until they completed the 4-month observation period or dropped out of the study was included in the model. Cox regression analysis was used to estimate the hazard ratio comparing the Echinacea and placebo groups.

In a second analysis the intervals between the end of both the first and second URI and the start of the second and third URI were included. The median time to subsequent URI was calculated. Cox regression analysis was used to determine overall differences in time between URIs in a child, after accounting for clustering in cases in which a child had two URIs. The power to detect a difference between the Echinacea and placebo treatment groups in this analysis was hampered by the fewer number of days contributed between the second URI and the end of the 4-month observation period (mean number of days of follow up: 53.8 days after URI 1 versus 43.6 days after URI 2).

Finally, in a third analysis the number of days between the start of the first URI, defined as the date on which the parent called the study staff to report a URI, and the start of a subsequent URI was calculated for the two treatment groups. The incidence rate of second URIs per week was calculated for both the Echinacea and placebo groups, by totaling the number of second URIs and dividing by the total time at risk of second URI for all children in each group. Cox regression analysis was used to determine the hazard ratio comparing the groups. For all analyses, \( p < 0.05 \) or 95% confidence intervals (CIs) of estimates of risk reduction that did not include zero were considered statistically significant.

The Institutional Review Boards of Children’s Hospital and Regional Medical Center of Seattle, Washington, and Bastyr University of Kenmore, Washington, approved the study. Signed written consent was obtained from the parents of study participants, and assent was obtained from participants who were \( \geq 7 \) years of age.

**RESULTS**

Of the 524 children who were enrolled in the study 426 had a verified first URI. Log books were not received for 25 first URIs in study participants. Thus 401 children were included in the primary analysis, with 204 randomized to placebo and 197 to Echinacea. Figure 1 illustrates the inclusion of participants in the primary and subsequent analyses. Table 1 summarizes the baseline characteristics of the 204 children randomized to placebo and the 197 children receiving Echinacea whose parents returned log books documenting the first URI. There were no appreciable differences between the two groups for all characteristics assessed. In addition there was no difference in the time to first URI in the two treatment groups (31.2 days in the placebo group versus 34.4 days in the Echinacea group, \( p = 0.23 \) with \( t \)-test).

After their first exposure to study medication 69.6% of the 204 children randomized to placebo and 55.8% of the 197 children randomized to Echinacea developed a subsequent URI during the observation period. The results of the Cox regression analysis indicated a statistically significant 28% reduced risk of subsequent URI in the children taking Echinacea in comparison to children taking placebo (\( p = 0.01; 95\% CI 8\%–44\% \) reduction in risk). Adjustment of the regression model for age, gender, number of siblings in the house, attendance in day care or school, smoker in the household, number of URIs in the previous year, concomitant medications taken during the first URI, and duration of the first URI did not substantially alter the hazard ratio.

Kaplan-Meier survival curves were created, with a “failure” indicating a subsequent URI had developed during the observation period (Fig. 2). The median time to subsequent URI...
URI was 38 days for children receiving placebo versus 46 days for children receiving Echinacea. The difference between the placebo and Echinacea curves was statistically significant with the log rank test ($p = 0.008$).

For the second analysis including both the time between first and second URIs and the time between second and third URIs, data from 407 patients were evaluated. This includes six children for whom a log book was not returned after the initial URI. In this analysis the median time to subsequent URI was 45 days in the placebo group versus 56 days in the Echinacea group. The results of the Cox regression analysis indicate a point estimate of a 16% reduction in the risk of subsequent URIs ($p = 0.066$; 95% CI 1% increase in risk to 30% reduction in risk). When all first URIs (with and without a log book) were included in the third analysis the median time to subsequent URI was 53 days in the placebo group and 65 days in the Echinacea group. The incidence rate of second URIs per week per child was 0.094 in the placebo group and 0.068 in the Echinacea group in the fall/winter season (incidence rate difference 95% confidence interval of $-0.047$ to $-0.007$). The results of the Cox regression indicate a statistically significant 31% reduction in the risk of subsequent URIs ($p = 0.003$; 95% CI 12%–46% reduction in risk).

**DISCUSSION**

The results of this study suggest that *Echinacea purpurea*, when taken as a treatment for an initial upper respiratory tract infection, may be effective in preventing subsequent URIs. In this secondary analysis of data from a randomized controlled treatment trial, children assigned to receive *Echinacea* treatment had a risk of subsequent URI that was 28% lower than children assigned to receive placebo ($p = 0.01$). A decrease of this magnitude in the number of URIs per year could have a large public health impact, given that up to 40% of visits to pediatricians in the winter months by children 1–5 years old are because of cough and URI symptoms.17

The data for this analysis come from the only known, large, placebo-controlled trial of *Echinacea purpurea* for the treatment of URI in children. The clinical trial was designed to determine the efficacy of *Echinacea* for the relief of symptoms of URIs.15 In summary, in this previous study there was no change in the duration or severity of URI with *Echinacea* use; compliance was high; and the blinding of the study medicine was adequate. The results presented here regarding prevention represent a serendipitous finding. Thus they should be interpreted with caution and need to be replicated.

URIs were defined based on symptoms reported by the parent during a telephone call. Symptoms were not confirmed via physician examination, nor were samples were taken to verify the presence of a virus. It is possible that the symptoms reported could be caused by new onset of allergic rhinitis after enrollment. Because *Echinacea* is not used for the treatment of allergic rhinitis, such misclassification of symptoms would bias the results toward the null.

Among published *Echinacea* prevention trials in adults at least six have included a placebo control group.9–14 Turner et al. tested the efficacy of *Echinacea* in a cold provocation model in which adult participants were given *Echinacea* ($n = 50$) or placebo ($n = 42$) for 2 weeks before a rhinovirus challenge and 5 days postchallenge.13 The results indicated that 13% fewer rhinoviral infections occurred in participants taking *Echinacea* ($p = 0.3$). Sperber et al. tested *Echinacea*...
purpurea juice in a cold provocation model.14 Echinacea was given 7 days pre- and 7 days post-intranasal inoculation with rhinovirus. The study reported a 24% difference in the number of individuals who developed cold symptoms ($p = 0.11$).14 Four of the studies used a dosing regimen of Echinacea for 8–12 weeks and then tabulated the number of participants developing an infection during the study period.9–12 In one of these studies the authors eliminated a large number of participants from the analysis for unknown reasons.10 In the remaining three studies the relative risk of infection after taking Echinacea ranged from 0.80 to 0.88 in comparison to placebo (corresponding to a reduction in the rate of infection in the Echinacea group by 12%–20%).9,11,12 However each of these studies used different products and the Echinacea did not statistically prevent URIs in comparison to placebo. Thus the results of these trials suggest a possible preventive effect of Echinacea species when given before viral challenge or given for 8–12 weeks in adults, which is weaker than yet consistent with the reduced risk of subsequent URI found in the children in the present study.

Several potential problems hamper the comparison of results from different Echinacea trials. First there are three species of Echinacea products commercially available: Echinacea purpurea, Echinacea pallida, and Echinacea angustifolia.7 Several methods of extraction are used to make Echinacea products, and currently the products are not standardized to a particular constituent. Manufacturers use different parts of the Echinacea plant when making their products (above-ground herb, root, or entire plant). Depending on the extraction method and the part and species of plant used, different constituents in varying amounts can be found in each extract. Thus the dosage and dosing protocols vary dramatically across studies. In addition some Echinacea studies used combination products, so it is unknown whether observed associations are caused by the Echinacea or the other ingredients in the product.7 Finally it is possible that Echinacea products may have different actions in adults and children; it may not be appropriate to generalize studies across age groups.

The available data suggest that although the Echinacea product used in this study was not effective in reducing the symptoms or severity of acute URIs, the ingestion of some Echinacea products may have been effective in reducing the occurrence of subsequent URIs in children. However until more research is conducted to delineate better the risk/benefit ratio of the use of Echinacea in preventing URIs in children, caution is advised. In this study it was found that Echinacea was well tolerated. Although no between-group difference in the total number of adverse events were noted, an increased occurrence of rash was reported among children whose URIs were treated with Echinacea.15 This may represent an allergic reaction to the herb. There have been case reports of serious allergic reactions, including anaphylaxis reactions after ingestion of Echinacea in adults with atopic disease.18 Future studies should be conducted to determine which Echinacea species, part of the Echinacea plant, extraction method, and dose regimen provide the greatest benefit/risk ratio for the prevention of URIs in children and adults. Additional studies to examine the biologic basis for the potential preventive effect against the occurrence of URIs are also needed.

In conclusion, Echinacea purpurea may be effective in reducing the occurrence of subsequent URIs in children.

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Conflict of Interest: Carlo Calabrese was on salary during 1999–2000 with Rexall Sundown Inc., which makes Echinacea products. Rexall Sundown did not supply the product used in this study. The other authors have no competing interests to declare.

REFERENCES


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