Xylitol Administered Only During Respiratory Infections Failed to Prevent Acute Otitis Media

Terhi Tapiainen, MD*; Leevi Luotonen, MD†; Tero Kontiokari, MD*; Marjo Renko, MD*; and Matti Uhari, MD*

ABSTRACT. Objective. As regular administration of xylitol had been effective in preventing acute otitis media (AOM) in children, we tested whether xylitol administered only at times of acute respiratory infection (ARI) reduces the occurrence of AOM.

Methods. Healthy children (N = 1277) were recruited from child care centers and randomized after screening with tympanometry to receive either control mixture (n = 212), xylitol mixture (n = 212), control chewing gum (n = 280), xylitol chewing gum (n = 286), or xylitol lozenges (n = 287) during an ARI. The trial was randomized and double blinded within the mixture and chewing gum groups. The parents began administering the products to their children at the onset of symptoms of ARI. The follow-up lasted until resolution of the symptoms or up to 3 weeks.

Results. A total of 1253 of the 1277 randomized children were eligible for the analysis. Altogether, 980 (78%) of 1253 children had at least 1 episode of ARI during the 4 months that the trial lasted. The occurrence of AOM during this episode was 34 (20.5%) of 166 in the xylitol mixture group, as compared with 32 (20.4%) of 157 among the children who received the control mixture. Among the older children who received control chewing gum, xylitol chewing gum, or xylitol lozenges, AOM was experienced by 24 (11.0%) of 218, 31 (14.1%) of 220, and 34 (15.5%) of 219, respectively. None of the differences between the groups was statistically significant.

Conclusions. Xylitol administered only during an ARI was ineffective in preventing AOM. *Pedi atrics 2002; 109(2). URL: http://www.pediatrics.org/cgi/content/full/109/2/e19; xylitol, otitis media, prevention, respiratory tract infection.

ABBREVIATIONS. AOM, acute otitis media; ARI, acute respiratory infection.

Xylitol is a 5-carbon polyol, ie, a sugar alcohol, that is widely distributed in plants and found in significant concentrations in plums, strawberries, and raspberries. It is an ideal sweetener for use in chewing gums in particular, because it is equal in sweetness to sucrose and has beneficial anticariogenic properties attributable to its effect on Streptococcus mutans.

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METHODS

Recruitment

The trial was conducted at the Department of Pediatrics, University of Oulu, Finland, between August 1999 and January 2000. The protocol was approved by the Ethical Committee of the City of Oulu. Written information was given to the parents, after which the purpose of the trial and its protocol were further explained in evening sessions at the child care centers. Only children whose parents gave their written informed consent were included in the trial.

Participants and Screening

The participants (N = 1366) were healthy children, aged 10 months to 7 years, who were recruited from 48 child care centers in the city of Oulu. Children who were receiving antimicrobial prophylaxis or were using creams to prevent otitis media were excluded. The children were screened with tympanometry (MiniTymp, Welch Allyn, Skaneateles Falls, NY) before the trial began, and all those who had normal tympano-
grams (A-curve) were accepted for participation in the trial. Those
with abnormal tympanograms (other than an A-curve) were
checked by pneumatic otoscopy. Any middle ear effusions were
treated before starting the trial, and children with current ARI but
healthy ears at the screening were reexamined after 1 week. Only
children with normal ear status and without current ARI (n = 1277) were eventually accepted.

Products Tested
The daily doses of control and xylitol products were equal to
those used in earlier trials showing the efficacy of continuous use
of xylitol.15 Children who were unable to chew gum were ran-
domized to receive 5 mL of either a control mixture containing 20
g/L xylitol diluted in water without any other sweeteners or a
mixture containing 400 g/L xylitol 5 times a day (a daily dose of
0.5 g and 10 g of xylitol, respectively). The mixtures were prepared
by the pharmacy at Oulu University Hospital. Parents were ad-
vised not to give their children any other xylitol preparations
during the follow-up. The mixtures were administered after meals
with a syringe during a period of 5 minutes to maintain a high
concentration of xylitol in the oral cavity for as long as practically
possible.

The children who were able to chew gum were randomized to
receive control chewing gum (daily dose 0.5 g of xylitol), xylitol
chewing gum (daily dose 8.4 g of xylitol), or xylitol lozenges (daily
dose 10 g of xylitol). A few children who were able to chew gum
were allocated to receive mixture because the sample size required
for the chewing gum groups had already been reached. Two
pieces of chewing gum or lozenges were chewed for at least 5
minutes 5 times a day after meals. Three of the doses were given
by the personnel at the child care centers during the day, and the
rest were given by the parents at home.

The products were thus given to children with normal ear
status and without current ARI (N = 1277) for use during the next
ARI episode. Compliance was monitored by asking the parents to
list the doses actually given on the daily symptom sheets and by
counting the unused pieces of chewing gum and lozenges re-
turned at the last appointment and measuring the volume of the
unused mixture.

Follow-Up and Diagnostic Criteria
Parents were instructed to start giving the product on the first
day of ARI, which was defined as the appearance of 1 or more of
the following symptoms: clear or purulent discharge from the
nasal, congestive nose, cough, conjunctivitis, throat ache, or ear
ache. The children usually had a fever as well (axillary tempera-
ture above 38.0°C) and in some cases vomiting. The first visit to
the clinic was conducted within 4 days of the onset of symptoms,
or for the same day if the child had earache. Tympanometry
(MiniTymp) was performed by 2 trained nurses at the clinic; the
tympanograms were classified by the method described by
Jerger.17 We have validated minitympanometry for the detection
of middle ear fluid.18 When tympanometry was normal (A-curve),
the child was examined weekly until resolution of the symptoms,
or up to 3 weeks; when it was abnormal (B, C, or positive
pressure curve) or the child had earache or discharge from the ear,
the child was examined by pneumatic otoscopy by a physician
engaged in the trial. The final diagnosis of AOM was based on a
finding of middle ear effusion in tympanometry (B, C, or positive
pressure curve) and always confirmed with pneumatic otoscopy.
The otoscopy was validated against the tympanometry and tympanometry. Whenever AOM was diagnosed, treatment with
antimicrobials was started and a follow-up was scheduled with
the family physician. Each child participated in the trial for 1
episode of infection only.

Eleven AOM episodes were first diagnosed by the clinic phy-
sician, 6 of which were checked at the clinic used for the trial;
AOM was confirmed in 5 cases. Five AOM cases of the total of 155
(37%) were not diagnosed at all at the trial clinic and were based
only on the family physician’s evaluation. These included 1 case of
purulent ear discharge. Dropouts were defined as children who
stopped visiting the clinic. Children who prematurely stopped
using the product assigned to them but continued to visit the clinic
were included in the analysis.

Study Design
The study was blinded as far as the mixture and chewing gum
groups were concerned but open as between the xylitol lozenge
and control chewing gum groups. The chewing gums were similar
in taste, but the xylitol mixture tasted sweeter than the control
mixture. Randomization was performed in blocks of 4 in the
mixture groups and in blocks of 3 in chewing gum and lozenge
groups, using a random number table to make the proportion of
participants in each study group approximately the same at each
child care center. Each child was given a unique participation
number at the time of the initial screening.

Sample Size
The calculations of sample size were based on the occurrence of
ARI and AOM in our previous trials, in which 75% of the children
experienced at least 1 ARI within a period of 3 months and the
occurrence of AOM during the first ARI in the control groups was
20% and 13% at the ages of 1 to 3 years and 4 to 6 years,
respectively.15 We estimated that if the follow-up time were ex-
tended 4 months, then >90% of the children would experience
at least 1 ARI. Because we considered a 45% reduction in the
occurrence of AOM to be clinically important and chose 0.05 type
I error (P value) and a power of 80%, it was calculated that sample
sizes of 203 younger children who received the mixture and 274 in
each group that received the chewing gum and lozenges were
needed (1220 children altogether).

Statistical Analysis
The mixture groups were analyzed separately from the chewing
gum and lozenge groups because of a higher incidence density of
AOM in young children. The children who dropped out (n = 24)
were excluded from the statistical analysis, but those who
prematurely stopped using the products but still visited the clinic (n = 35) were included. A normal standard deviation test was
used to compare the proportions of children with AOM diagnosed
between the control group and group that received xylitol. The
Kaplan-Meier method was used to analyze the time that elapsed
before the first AOM during the 4-month trial. The children who
dropped out contributed days at risk to the cumulative occurrence
analysis for as long as they continued to participate. The log rank
test was used to test the differences in time that elapsed before the
first AOM between the control and xylitol groups. Most statistical
analyses were performed using SPSS 9.0 for Windows 98 (SPSS,
Inc, Chicago, IL), except for the standard deviation test, which
used Arcus Quickstat (CamCode, Ashwell, UK).

RESULTS
Altogether, 1277 children were eligible for the trial, ie, they had normal tympanometry and no current
ARI symptoms and were randomized to receive the control mixture (n = 212), the xylitol mixture (n = 212),
the control chewing gum (n = 280), the xylitol chewing gum (n = 286), or the xylitol lozenges (n = 287).
These groups did not differ regarding demographic features, known AOM risk factors, or AOM
history (Table 1). There were 24 dropouts, which left 1253 children eligible for analysis (Fig 1, Table 2).
Altogether, 980 of these (78%) experienced ARI and visited the study clinic. The proportion of children
with ARI was similar in all of the groups (Fig 1).

AOM occurred in 32 (15.2%) of 211 children in the control mixture group and in 34 (16.4%) of 207 children
in the xylitol mixture group, ie, in 32 (20.4%) of 157 and 34 (20.5%) of 166 of the cases of ARI, respec-
tively (Table 3). Among the older children, it was
diagnosed in 24 (8.7%) of the 277 children who were
randomized to receive control chewing gum, 31
(11.2%) of the 277 in the xylitol chewing gum group,
and 34 (12.1%) of the 281 in the xylitol lozenge group,
suggesting 24 (11.0%) of 218, 31 (14.1%) of 220, and
34 (15.5%) of 219 of the corresponding children with
ARI (Table 4). None of the differences was statistically significant \((P = .18-.98; \text{Tables 3 and 4})\). The occurrence of AOM during the 4-month trial was comparable in time in all of the groups and did not differ in its timing during ARI.

Approximately 80% of the products were administered as intended in all treatment groups, and only a few children \((n = 37)\) stopped taking them prematurely, except in the group that received the xylitol lozenges, in which 20 (9%) of 219 children did so, mainly because they disliked them or experienced abdominal discomfort (Table 2). All but 2 of the children whose parents stopped giving them the product continued to visit the clinic (Table 2). In the case of 20% of the ARI episodes, administration of the products was started later during the infection than had been intended, and to test whether the timing of xylitol ingestion could have affected the results, we also performed the analysis separately for those participants who received the product on the first day of ARI and received at least 80% of the intended doses, but there were no differences between the groups that received control or xylitol products in this analysis, either (data not shown).

**DISCUSSION**

After the finding that regular use of xylitol is effective in reducing AOM, we have been looking for the easiest way to implement xylitol prophylaxis in clinical practice. The 2 main alternative approaches to the problem were either to reduce the number of daily doses or to focus the prophylaxis on the times of greatest AOM risk (ie, ARI episodes). As we thought that it would be most convenient for the families to give their children xylitol only during ARI, we decided to test this option. The trial nevertheless demonstrated that such a regimen was ineffective in preventing AOM.

**TABLE 1. Baseline Characteristics of the Participants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mixture</th>
<th>Chewing Gum</th>
<th>Lozenge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control ((n = 212))</td>
<td>Xylitol ((n = 212))</td>
<td>Control ((n = 280))</td>
</tr>
<tr>
<td>Number of girls</td>
<td>111</td>
<td>106</td>
<td>131</td>
</tr>
<tr>
<td>Mean (SD) age (y)</td>
<td>3.7 (1.9)</td>
<td>3.5 (1.8)</td>
<td>4.8 (1.2)</td>
</tr>
<tr>
<td>Breastfeeding at least 6 mo (%)</td>
<td>63.5</td>
<td>68.1</td>
<td>64.4</td>
</tr>
<tr>
<td>Current use of a pacifier (%)</td>
<td>21.7</td>
<td>18.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Mean (SD) duration of child care (mo)</td>
<td>18 (18)</td>
<td>18 (17)</td>
<td>26 (18)</td>
</tr>
<tr>
<td>Adenoidectomy performed (%)</td>
<td>24.0</td>
<td>24.5</td>
<td>33.5</td>
</tr>
<tr>
<td>Previous history of AOM (%)</td>
<td>0 attacks</td>
<td>18.4</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>1–5 attacks</td>
<td>50.0</td>
<td>42.7</td>
</tr>
<tr>
<td></td>
<td>&gt;5 attacks</td>
<td>31.6</td>
<td>49.4</td>
</tr>
<tr>
<td>Current tympanostomy tubes (%)</td>
<td>6.1</td>
<td>5.7</td>
<td>3.6</td>
</tr>
</tbody>
</table>

SD indicates standard deviation.

**Fig 1.** Design of the trial. After screening, the children were allocated to 2 groups according to their ability to chew gum and then randomized to receive either a control mixture or a xylitol mixture in the case of the younger children or control chewing gum, xylitol chewing gum, or xylitol lozenges in the case of the older children. These products were administered to them during their next episode of ARI. The numbers of children who experienced ARI during the 4 months of the trial (numbers of dropouts in parentheses) and numbers of AOM episodes are given for each group.
Our finding is analogous to that regarding antimicrobial prophylaxis, which is effective in preventing AOM when applied continuously but ineffective when applied intermittently during ARI.\textsuperscript{14,19–22} Bacterial adherence to pharyngeal cells is enhanced during viral infection, and the incidence of otitis media pathogens in the nasopharynx is increased at such times.\textsuperscript{23–25} Viral infection leads to changes in bacterial adherence from the first day of inoculation onward, ie, 1 to 3 days before the appearance of symptoms,\textsuperscript{23,26} which may explain the ineffectiveness of intermittent prophylaxis,\textsuperscript{22} because preventive measures initiated in response to symptoms of viral infection miss the incubation period and thus may be too late.

It could be speculated that the lack of efficacy observed in this trial was attributable to a difference in the viral cause of the respiratory infections that lead to AOM relative to our previous trials.\textsuperscript{27} This is unlikely, because all of these trials were performed during the same epidemiologic period, in autumn, and the occurrence of AOM remained similar in time throughout the 4-month trial, showing that even if there had been any changes in the epidemiology of ARI, these could not have significantly altered the occurrence of otitis media.

Parents’ hesitation to start the prophylaxis in response to minor or gradually developing symptoms of ARI could have influenced the results, but the prophylaxis was not effective even with optimal timing of the xylitol prophylaxis. There were no clear differences between the control and xylitol groups in abdominal discomfort or in the number of children who stopped taking the product, with the exception of the xylitol lozenge group, in which abdominal discomfort and dislike of the product was common. The xylitol dosing schedule was accepted well by the parents, and compliance during the trial was good and comparable with that achieved in the trials in which xylitol was used regularly.\textsuperscript{15,16} Therefore, the lack of efficacy could not have been attributable to problems of compliance.

Although our goal is to find the easiest, most effective way of implementing xylitol prophylaxis, it should be remembered that xylitol has been used successfully on a continuous basis without problems.

### Table 2. Reasons for Dropouts or Stopping Administration of the Products by the Treatment Group

<table>
<thead>
<tr>
<th>Mixture</th>
<th>Control (n = 212)</th>
<th>Xylitol (n = 212)</th>
<th>Control (n = 280)</th>
<th>Xylitol (n = 286)</th>
<th>Xylitol (n = 287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of dropouts*</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Parents got tired</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Child disliked the product</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other antibiotics for ARI</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Left the area</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Administration discontinued†</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Child disliked the product</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Total number of children</td>
<td>153</td>
<td>9</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Not included in the analysis.
† Continued visiting the clinic and included in the analysis, except for 2 children mentioned as dropouts.

### Table 3. Proportions of Children With AOM Among Those Receiving Mixtures During an ARI

<table>
<thead>
<tr>
<th>Control Mixture (n = 211)</th>
<th>Xylitol Mixture (n = 207)</th>
<th>Difference</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children with ARI (%)</td>
<td>157 (74)</td>
<td>166 (80)</td>
<td>-1.2</td>
<td>-8.3 to 5.8</td>
</tr>
<tr>
<td>Total number of children with AOM</td>
<td>32</td>
<td>34</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>AOM (% of all children)</td>
<td>15.2</td>
<td>16.4</td>
<td>-0.1</td>
<td>-8.9 to 8.8</td>
</tr>
<tr>
<td>AOM (% of children with ARI)</td>
<td>20.4</td>
<td>20.5</td>
<td>0.1</td>
<td>8.9 to 11.0</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

### Table 4. Proportions of Children With AOM Among Those Receiving Control Chewing Gum, Xylitol Chewing Gum, or Xylitol Lozenges During an ARI

<table>
<thead>
<tr>
<th>Chewing Gum</th>
<th>Xylitol Lozenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 277)</td>
<td>Xylitol (n = 277)</td>
</tr>
<tr>
<td>Number of children with ARI (%)</td>
<td>218 (79)</td>
</tr>
<tr>
<td>Total number of children with AOM</td>
<td>24</td>
</tr>
<tr>
<td>AOM (% of all children)</td>
<td>8.7</td>
</tr>
<tr>
<td>AOM (% of children with ARI)</td>
<td>11.0</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
of compliance.\textsuperscript{15,16} Children accept it well and even consider it fun when it is administered after meals, almost like a dessert. The number of pieces of chewing gum needed to prevent 1 episode of AOM (5 daily doses of 2 pieces) may sound high and has been criticized,\textsuperscript{28} but the good compliance achieved in our clinical trials with frequent dosing of xylitol suggests that this may be more of a problem in the minds of physicians than it really is for the parents and their children.

We conclude that intermittent xylitol prophylaxis during ARI was ineffective in preventing AOM. This is contrary to the situation with continuous xylitol prophylaxis, which effectively prevents AOM.\textsuperscript{15,16}

ACKNOWLEDGMENTS

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The use of xylitol in treating respiratory infections (Uhari M, Kontiokari T, inventors) is patented in the United States (US patent numbers 5719196, February 17, 1998, and 6066677, May 23, 2000).

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