Review Article

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Use of xylitol in preventing acute otitis media: a meta-analysis

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Abstract

Objective: *To examine the available data on the effect and the dosing regimen of xylitol in preventing Acute otitis media (AOM) in children.* ***Methods:*** *Primary studies were extracted from 3 databases (MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) using the Ovid platform, limited to papers published from 1960 to 2008 October. The key words used included xylitol and otitis.* ***Results:*** *Meta-analysis was performed for the 4 relevant RCTs. The overall aggregated risk difference was -0.0378 (95% confidence interval -0.0892 to 0.0135, p=0.1489). The aggregated risk difference for the xylitol 5 times daily group was -0.0933 (p=0.0002) and was statistically significant. However, the aggregated risk differences were 0.038 (p=0.1618) and -0.0076 (p=0.7831) for the xylitol 3 times daily group and the intermittent xylitol during acute respiratory infection group respectively, which were both statistically insignificant.* ***Conclusion:*** *The overall aggregated risk difference was not statistically significant when combining results from studies using different xylitol regimen including both regular and intermittent regimens. However, there is evidence to support that xylitol, given with a regular 5 times daily regimen, significantly reduces the occurrence of acute otitis media in one ethnic group.*

Keywords: Acute otitis media (AOM), Child, Xylitol

Introduction

Xylitol is a 5-carbon polyol, which is widely distributed in plants such as plums, strawberries, and raspberries.[1] With its equal sweetness to sucrose,[1] as well as its beneficial anticariogenic properties attributable to its effect on *Streptococcus mutans*,[2,3] it is considered to be an ideal sweetener for use in chewing gums. *Streptococcus mutans* are unable to use xylitol, resulting in a toxic effect to them.[4,5] Xylitol also reduces the growth of Streptococcus pneumoniae, the main pathogen implicated in acute otitis media (AOM).[6] In addition, xylitol restricts the adherence of both Streptococcus pneumoniae as well as Haemophilus influenzae, the other important AOM pathogen, to nasopharyngeal cells.[7]

Recurrence of acute otitis media is common in children, and surgical procedures such as tympanostomy and adenoidectomy seem to have only a minor impact on recurrences.[8] Therefore, prevention is believed to be the best means of solving the problems associated with recurrence of AOM.[9-12] A new pneumococcal vaccine has been developed, but it was reported to have an efficacy of <10% in reducing recurrences of AOM.[13] Prophylactic use of antimicrobials has the desired effect, but it is liable to lead to the development of antimicrobial-resistant bacteria.[10,14] Therefore, new approaches to AOM prevention are needed. The purpose of the current review is to examine the current available data concerning the effect of xylitol in preventing acute otitis media.

Methods

Three databases (MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) were searched using the Ovid platform by one of the authors, CHC. The search strategy was aimed as high specificity rather than high sensitivity, and it was listed below:

Search strategy

1. xylitol.mp;
2. otitis.mp;
3. 1 and 2;
4. remove duplicates from 3;
5. limit 3 to "review articles";
6. 4 not 5.

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The search were limited to papers published from 1960 to 2008 October. Twenty papers were identified and two authors (CHC and YCC) independently reviewed the paper for relevance. The inclusion criterion was any randomized controlled trial comparing the effect of preventing acute otitis media between the treatment group, i.e. xylitol in any oral form and the placebo group. The primary outcome measure was the occurrence of acute otitis media during the entire follow-up period of the study. There were four relevant articles of RCTs selected according to the inclusion criteria. In the current analysis, the random effect model was used because there was significant heterogeneity among our pooled studies (Q=13.95, d.f.=5, p=0.1489).

Results

Four relevant articles of RCTs were selected for analysis according to our inclusion criteria. It was first reported from Finland that xylitol had a preventive effect against acute otitis media by Uhari et al.[15] They performed a 2-month double blind randomized trial with 306 day care children (mean age of 5 years), who were all healthy normal children recruited from eleven ordinary day care nurseries in the city of Oulu. Xylitol chewing gum was given 5 times per day (daily dose of 8.4 g) for 2 months in the xylitol group while sucrose chewing gum was given in the control group. The diagnostic criteria for AOM included symptoms and signs of acute respiratory infection and simultaneous signs of middle ear effusion, i.e. a cloudy tympanic membrane or impaired tympanic membrane motility in pneumatic otoscopy. During the 2-month monitoring period, at least one event of AOM was experienced by 19/157 (12.1%) children in the xylitol group, compared with 31/149 (20.8%) in the control group (difference 8.7%; 95% CI 0.4% to 17.0%; p=0.04). Significantly fewer antimicrobials were prescribed among those receiving xylitol: 29/157 (18.5%) children had at least one period of treatment versus 43/149 (28.9%, difference 10.4%; 0.9% to 19.9%; p=0.032).

Another randomized controlled trial was performed in the same centre in Finland again by Uhari et al, recruiting 857 healthy children from day care centres.[16] Xylitol was given in chewing gum, lozenges or in a mixture 5 times per day for 3 months. The daily dose was 8.4 g in the xylitol chewing gum group, 10 g in the xylitol lozenges group, 10 g in the xylitol mixture group and 0.5 g in the control group. They found that at least one event of AOM was experienced by 46/159 (29%) children receiving xylitol syrup, compared with 68/165 (41%) children in the control group (difference 30%; 95%CI 4.6% to 55.4%, p=0.028). Likewise, the occurrence of AOM decreased by 40% (95% CI: 10% to 71.1%, p=0.025) in children receiving xylitol chewing gum compared with control subjects. The occurrence of AOM decreased by 20% in children receiving xylitol lozenge, but the difference was not statistically significant (95% CI: -12.9% to 51.4%, p=0.30). Thus, the occurrence of AOM during the follow-up period was significantly lower in those who received xylitol syrup or chewing gum, and these children required antimicrobials less often than controls.

Hautalahti et al performed a 3-month double-blind randomized controlled trial with 663 healthy day care children to test whether xylitol administered 3 times per day, a more convenient dosing regimen, reduced the occurrence of AOM.[17] It was performed between August 2001 and January 2002 during the respiratory infection season. Xylitol was given in chewing gum or in a mixture 3 times per day for 3 months, with the daily dose of 9.6 g in the xylitol group and 0.5 g in the control group. It was found that at least one AOM episode was diagnosed in 94/332 (28%) children who received xylitol products, compared with 98/331 (30%) in the control group. A total of 142 episodes of AOM were diagnosed in the control group compared with 156 in the xylitol group. The differences were not statistically significant. It was concluded that xylitol given regularly 3 times a day for 3 months during the respiratory infection season failed to prevent AOM.

Tapiainen performed another RCT to test whether xylitol administered only at times of acute respiratory infections (ARI) reduced the occurrence of AOM,[18] with 1,277 healthy children recruited from child care centres. Xylitol was given in chewing gum, lozenges or in a mixture, starting at the onset of symptoms of ARI, with the daily dose being 8.4 g in the xylitol chewing gum group, 10 g in the xylitol lozenges group, 10 g in the xylitol mixture group and 0.5 g in the control group. During the 4-month trial, it was found that the occurrence of AOM during acute respiratory infection was 34/166 (20.5%) in the xylitol mixture group, as compared with 32/157 (20.4%) in the control group. Among the older children, AOM was experienced by 24/218 (11%) children in control group, 31/220 (14.1%) children receiving xylitol chewing gum, and 34/219 (15.5%) children receiving xylitol lozenge. None of the differences between the groups was statistically significant. Therefore, it was concluded that xylitol administered only during an ARI was ineffective in preventing AOM.

Combining all the results from the 4 relevant RCTs, the overall aggregated risk difference was -0.0378 (95% confidence interval -0.0892 to 0.0135, z=-1.4433, p=0.1489). The aggregated risk difference for the treatment regime of 5 times per day xylitol group was -0.0933 (95% confidence interval -0.1428 to -0.0438, z=-3.6959, p=0.0002). The aggregated risk difference for the 3 times per day xylitol group was 0.038 (95% confidence interval -0.0152 to 0.0912, z=1.399, p=0.1618). The aggregated risk difference for the 5 times per day xylitol during acute respiratory infection group was -0.0076 (95% confidence interval -0.0619 to 0.0467, z=-0.2752, p=0.7831). A forest plot is shown in Figure 1.

Discussion

In the current meta-analysis, the overall aggregated risk difference was -0.0378 (95% confidence interval -0.0892 to 0.0135, p=0.1489), which was not statistically significant. In the two RCTs by Uhari et al, regular courses of xylitol were given during the trials.[15,16] It was proposed that the mechanism of action of xylitol in preventing AOM was best explained by its local inhibitory effects on the growth of pneumococci and the inhibition of the adhesion of both pneumococci and H influenzae in the nasopharynx.[6,7,16] In contrast to the regular xylitol regimen by Uhari, Tapiainen used an intermittent course of xylitol only given during episodes of acute respiratory infection during the trial,[18] resulting in an absence of beneficial effect in preventing the occurrence of AOM, with the risk difference of -0.0076 (95% confidence interval -0.0619 to 0.0467, z=-0.2752, p=0.7831). There may be lack of time to develop sufficient protective effect of xylitol if it is only given at the onset of acute respiratory infection, when the viral load and bacterial growth have already started to rise quickly during acute respiratory infection. This difference in the xylitol regimens may account for the discrepancy between the risk difference from the Uhari studies and the risk difference from the Tapiainen trial. In fact, because of the significant difference of the treatment regimen between these RCTs, they should not be put into the same meta-analysis to generalize the overall effect of xylitol. Therefore, it is more appropriate to analyze these two groups of studies separately. The aggregated risk difference for the xylitol given with a regular 5 times daily regimen was -0.0933 (95% confidence interval -0.1428 to -0.0438, z=-3.6959, p=0.0002), which was

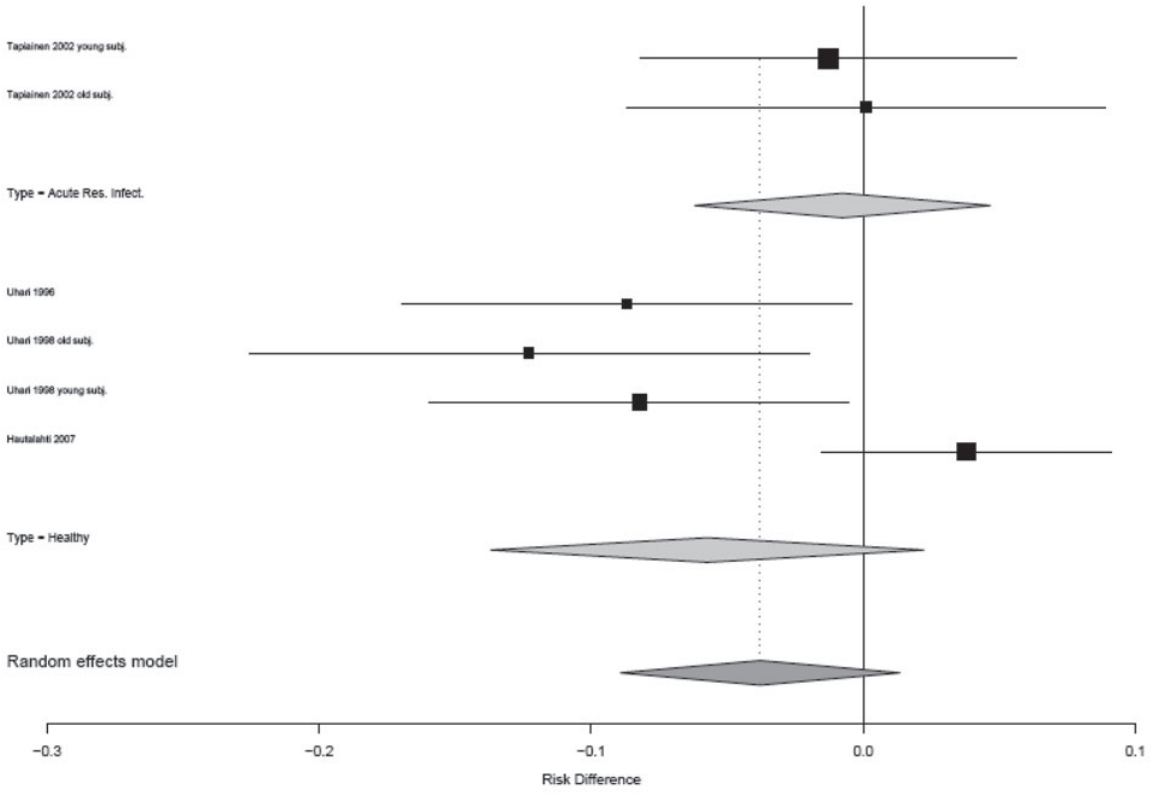

Figure 1. Forrest plot of the 4 RCTs.

statistically significant. Hence, there was evidence to support that the use of regular xylitol 5 times daily significantly reduced the occurrence of AOM in children.

A more convenient dosing regimen of xylitol, 3 times daily, was used by Hautalahti,[17] with no beneficial effect on preventing AOM demonstrated. The risk difference was 0.038 (95% confidence interval -0.0152 to 0.0912, z=1.399, p=0.1618), which was not statistically significant. Using a less frequent dosing regimen meant a longer time between the doses. The bacteria had subsequently more time to recover before the next scheduled dose. And the antiadhesive effect of xylitol is probably impaired when the time interval between doses is extended.[17] In fact, because of the significant difference of the treatment regimen between this RCT and the previous RCTs using more 5 times daily regimen, they should not be put into the same meta-analysis to generalize the overall effect of xylitol.

On the other hand, the 2 RCTs that showed significant beneficial effects of xylitol were both conducted by Uhari et al in the same centre in Finland.[15,16] There have been no other similar trials performed in other countries for other populations. Whether the study results were only applicable to certain populations have to be looked into. Studies with similar dosing regimen used in the RCTs by Uhari et al should be performed in other countries for other populations to verify the generalisibility of the study results.

Recurrence of acute otitis media is common in children. A certain proportion of participants in the RCTs by Uhari et al had previous history of acute otitis media as well as complications such as middle ear effusion, and some of them even required surgical intervention for treating complication. Whether these factors would or would be influenced with the xylitol treatment remained unclear. Further studies are needed to address on these issues as well.

Conclusion

In the current meta-analysis, there is evidence to support that xylitol, given with a regular 5 times daily regimen, significantly reduces the occurrence of acute otitis media. However, the overall aggregated risk difference was not statistically significant when combining results from all studies that employed different xylitol regimens. The limited number of relevant RCTs warrants more studies to be undertaken concerning the beneficial effects of xylitol on the prevention of acute otitis media.

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