Original Article

Xylitol nasal preparations in sinonasal disease: a literature review and meta-analysis

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Background: Xylitol is a naturally occurring chemical compound with inherent antimicrobial properties. It has recently been found to be an additive to saline solution in commercially available nasal sprays and rinses. The objective of this review was to assess the effectiveness of xylitol nasal preparations in the treatment of sinonasal disease.

Methods: A systematic review was performed with Medline, EMBASE and CENTRAL searched for randomised controlled trials (RCTs) where xylitol was compared to nasal saline additives in the treatment of sinonasal disease. The primary outcome was the difference in 22-item Sinonasal Outcome Test (SNOT-22) score between the xylitol and saline groups before and after use. Data for the SNOT-22 score was pooled using random effects model. The results were then compared against the predefined Minimal Clinically Important Difference (MCID) value for the SNOT-22 score. Subgroup analysis was performed between post-operative patients versus non-operative patients. The post-operative subgroup was further divided into an endoscopic sinus surgery (ESS) and a non ESS subgroup.

Results: Seven eligible RCTs were identified from our search, of which 5 were included into our meta-analysis. The overall pooled mean difference in SNOT-22 scores between xylitol versus saline was −7.77 (95% CI: −10.89 to −4.65, P<0.00001). A random effects model was used to pool mean difference given significant heterogeneity seen across all included studies (I^2=85%). In the post-operative ESS group, the pooled mean difference was −11.23 (95% CI: −12.97 to −9.48, P<0.00001). In the non-surgical group, the pooled mean difference was −4.99 (95% CI: −8.96 to −1.02, P=0.01). In the post-operative non ESS group there was no statistically significant difference. Compared to the predefined MCID score of 8.9, the post-surgical ESS subgroup met this threshold with a score of 11.23, whereas the non-surgical subgroup failed to meet the threshold with a score of 4.99.

Conclusions: Xylitol may be an effective agent of choice in the treatment of sinonasal disease in post-surgical ESS patients. There may also be a role for the use of xylitol in non-surgical patients if nasal symptoms were the main contributor to their overall symptomology.

Keywords: Xylitol; nasal; sinusitis; 22-item Sinonasal Outcome Test (SNOT-22)

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Introduction

Xylitol is a naturally occurring chemical compound which exists as a five-carbon sugar. It has been used as a sugar substitute for products such as chewing gum, toothpaste and confectionary (1). Its metabolism is free from the influence of insulin therefore has negligible effects of blood sugar.

Xylitol has been shown to exhibit antimicrobial properties with several studies demonstrating that this is owed to its inherent ability to enhance the innate immune system by altering the salt concentration of the airway surface liquid thereby increasing the effect of endogenous antimicrobials such as lysozymes, lactoferrin and beta defensins (2,3). It also acts as an anti-biofilm agent through inhibition of key enzymes (4-6).

From a rhinologic perspective, xylitol has shown promise in the treatment of sinonasal disease with animal studies demonstrating its efficacy in reducing chronic rhinosinusitis (CRS) biofilms (7) and enhancing bacterial killing in nasal and sinus mucosa (8). Specifically, it has effects on several pathogens commonly implicated in sinonasal disease, directly affecting the growth of *Streptococcus pneu*moniae and *Haemophilus influenzae* whilst being able to dissolve the biofilm structure of *Pseudomonas aeruginosa*. As a result, xylitol has now been found as an additive to saline solution in commercially available nasal sprays and sinus rinses (9).

CRS is a prevalent condition in Australia, it carries a high burden on our healthcare system accounting for 1.4% of all general practice encounters. It has been estimated that the yearly cost of CRS in terms of lost productivity is approximately $10,000 AUD per patient per annum (10). Despite significant advancements in medical and surgical treatments a high burden of treatment refractory symptoms and recurrence remain (11).

The goal of this review is to assess evidence pertaining to xylitol nasal preparations and its efficacy in the treatment of sinonasal disease in both pre and post-operative patient groups. We present the following article in accordance with the PRISMA reporting checklist (available at https://www.theajo.com/article/view/10.21037/ajo-21-45/rc) (12).

Methods

A systematic review of the literature relating to the use of xylitol in treating sinonasal disease was performed.

Searching

We performed an electronic search of the literature via Medline, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) from their respective dates of inception up until September 2021. The electronic search was performed using a combination of keywords consisting of 'xylitol', 'nasal', 'sinus', 'sinusitis' and 'rhinitis'. Two reviewers independently screened the search results and the bibliographies of each article were also hand searched for any further relevant trials. Duplicate results were removed. No automation tools were used in this process.

Population inclusion criteria comprised of adult patients with sinonasal disease (rhinosinusitis with or without nasal polyposis, rhinitis or inferior turbinate hypertrophy). The intervention consisted of xylitol additives to nasal topical medications in comparison to any other nasal preparations including saline or conservative treatment. Only randomised controlled trials were included in this review.

Outcome measure

The primary outcome measure was the difference in 22-item Sinonasal Outcome Test (SNOT-22) scores between the intervention (xylitol) versus the comparison (saline) group before and after use. The SNOT-22 is a validated questionnaire designed to assess the burden of CRS symptomology. The questionnaire consists of 22 questions each scored on a Likert scale ranging from 0 (no problem) to 5 (Problem as bad as it can be). The higher the SNOT-22 score the higher the burden of disease and vice versa. The mean SNOT-22 scores between pre-and post-treatment from the Xylitol group would then be subtracted from equivalent score from the Saline group giving a quantifiable measure of Xylitol's effects. A more negative value would suggest xylitol having a greater effect whilst a more positive value would suggest that saline has a greater effect.

Our results would then be compared against the Minimal Clinically Important Difference (MCID) value for the SNOT-22 score. The MCID score is defined as the minimal required change in a score on an outcome instrument (in our case SNOT-22) that corresponds to a patient's perception of beneficial change (13). The MCID value for SNOT-22 was defined a priori as 8.9 (14) with later similar studies corroborating this value (15,16).

Selection and data collection process

Non-English texts were excluded as well as studies which did not utilise validated outcome measures such as the SNOT-22. A risk of bias assessment was performed across all included studies by using the revised Cochrane risk-of-bias tool for randomised trials. Full text articles for each of the relevant studies were obtained for further review and data collection. Data was compiled on study design (duration, inclusion and exclusion criteria, population size, intervention type and control), population characteristics and outcome measures (mean difference in SNOT-22 score).

Statistical analysis

In instances where the standard deviation or 95% confidence intervals were not provided in the text, they were calculated from the provided data using the relevant statistical formulae. Data meta-analysis was performed using Review Manager 5.4. The SNOT-22 score mean difference was pooled using a random effect model. Statistical heterogeneity between the studies was evaluated using the I^2 statistic. A subgroup analysis was performed with the outcome measure compared between patients who have undergone surgery versus those who have not. We further divided the post-surgical subgroup into patients who have had endoscopic sinus surgery (ESS) compared to other operative procedures such as septoplasty. Analysis was planned to be performed using a random effects model with a 95% confidence interval and $P<0.05$ pre-specified as being statistically significant.

Results

A total of 34 articles were identified after our electronic search, 5 of the articles were excluded due to being duplicates. Given the small number of articles yielded from our search the full text of 29 articles were then reviewed, of which 22 were excluded. Reasons for exclusion included, non-randomised control trial, animal/*in vitro* studies and a paediatric study population. A total of 7 eligible RCTs were identified however 2 had to be excluded from further analysis as unlike the other RCTs, they did not use the validated and comparable SNOT-22 score as their outcome measure to assess intervention effect.

Cingi *et al*. used a visual analog scale (VAS) where they asked participants to mark their overall 'sinonasal wellbeing' as well as assessing quality of life by means of using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). It should be noted that they also employed rhinomanometry as an objective measure of treatment effect (17), however this was the only study which employed this method and therefore the results would not have been comparable across the other groups. Sanchez-Gonzalez *et al*. used the VAS score as well as the daily symptoms score (DSS) as their outcome measure (18).

Therefore, a total of 5 articles were identified for inclusion into our analysis. The PRISMA flow diagram for identification of studies for inclusion is shown in *Figure 1* (12).

The characteristics of the included studies have been summarised and can be found in *Table 1*. Three out of the 5 included studies were blinded. Hayer *et al.* did not attempt to blind their participants as they reported that participants could taste the difference in irrigation solutions, the outcome assessors, data entry personnel and statistician were however blind to the allocation group (19). The xylitol solutions used were either 1.6% or 5% wt/vol, the mode of delivery remained consistent across all studies. There was considerable variability in frequency of treatment ranging from once daily to three times daily irrigations and similarly regarding duration of treatment with the shortest trial lasting 26 days and the longest trial lasting 26 weeks.

A risk of bias assessment was performed across all the included studies with use of the modified Cochrane Collaboration tool. Bias outcome was assessed as a judgement (either high, low or unclear) across multiple domains through which bias may be introduced into the trial (20). The results of which can be found in *Table 2*.

All the included studies adequately described their method of random sequence allocation to produce comparable intervention and control groups, and this was demonstrated in the comparable demographic characteristics as shown in each of the articles.

Selective reporting bias was a domain that was assessed as being unclear across all the trials as there was insufficient data to permit judgement. We did not find any specific mention in any of the study protocols which addressed whether the trial would be analysed in concordance with the finalized pre specified plan before the outcome data was available for analysis. It should be noted however that according to the risk of bias assessment tool that we used, most studies were expected to fall into this category.

There was a total of 5 RCTs that included the mean change in SNOT-22 score between xylitol and saline as their outcome measure, thereby permitting a meta-analysis

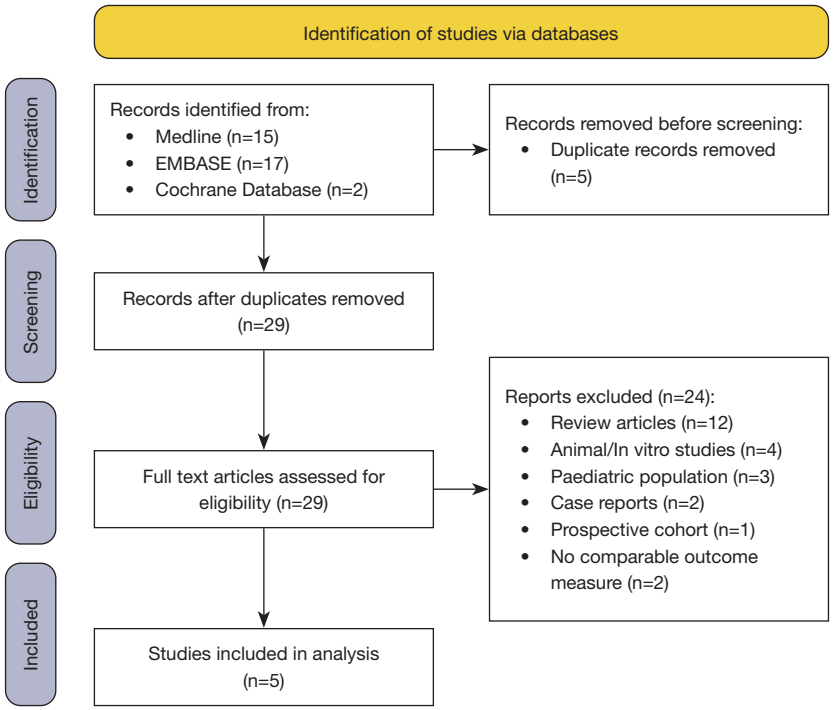

Figure 1 PRISMA flow diagram for identification of studies for inclusion. RCTs, randomised controlled trials.

to be performed (*Figure 2*). The overall pooled mean difference in SNOT-22 scores between xylitol versus saline was –7.77 (95% CI: –10.89 to –4.65, P<0.00001). A random effects model was used to pool mean difference given significant heterogeneity seen across all included studies (I^2=85%).

Furthermore, a subgroup analysis was performed between post-operative patients versus non operative patients. The post- operative patients were divided into an ESS group and a non ESS group. Kim *et al.* was the only trial that included a post-surgical patient population that did not have ESS, they underwent a septoplasty (21).

In the post-operative ESS group, the pooled mean difference in SNOT-22 scores between xylitol versus saline was –11.23 (95% CI: –12.97 to –9.48, P<0.00001). A random effects model was used to pool mean difference given moderate heterogeneity in the included studies (I^2=37%). In the post-operative non ESS group, the mean difference in SNOT-22 score between xylitol versus saline was 0.40 (95% CI: –7.47 to 8.27) this result was not statistically significant. In the non-surgical group the pooled mean difference in SNOT-22 scores between xylitol versus saline was –4.99 (95% CI: –8.96 to –1.02, P=0.01). A random effects model was used to pool mean difference given significant heterogeneity in the included studies (I^2=51%).

Compared to the predefined MCID score of 8.9, the post-surgical ESS subgroup met this threshold with a score of 11.23, whereas the non-surgical subgroup failed to meet the threshold with a score of 4.99. The post-surgical non ESS subgroup fell well short of the MCID score with a positive mean difference score of 0.40, suggesting that xylitol does not make a significant difference in this subgroup.

Discussion

Xylitol has several advantages, it is cost effective, readily available over the counter and has been proven to be safe for human use (22). It has a small side effect profile and was reported across all studies to be well tolerated by the participants; no participants were removed from trials as a result of xylitol side effects.

This review identified several RCTs which assessed the effectiveness of xylitol nasal preparations in the treatment of sinonasal disease. The meta-analysis and consequent subgroup analysis found evidence that xylitol may be more effective than normal saline at reducing the burden

Table 1 Summary of included trials comparing Xylitol to saline in the treatment of sinonasal disease

Authors [year]	Study design	Population [n]	Solutions used	Method of delivery	Duration of treatment	Outcome measures
Weissman *et al.* [2011]	Randomised double blinded crossover trial (xylitol *vs.* saline)	CRS patients [20]	Xylitol (5% wt/vol); Saline (0.9% wt/vol)	Irrigation	3 days washout prior to commencement of treatment. Once daily irrigations for 10 days followed by 3 days washout and once daily irrigation with alternate irrigant	SNOT-22 score; VAS score
Lin *et al.* [2017]	Randomised double blinded trial (xylitol *vs.* saline)	CRS patients with previous ESS [30]; 15 per arm	Xylitol (5% wt/vol); Saline (0.9% wt/vol)	Irrigation	Once daily irrigations for 30 days	SNOT-22 score; VAS score; Nasal NO; iNOS mRNA
Kim *et al.* [2019]	Randomised double blinded crossover trial (xylitol *vs.* saline)	Patients with sinonasal disease who underwent septoplasty/ ESS/both [100]; 50 per arm	Xylitol (1.6% wt/vol); Saline (0.9% wt/vol)	Irrigation	Three times daily irrigations for 14 days followed by 7 days washout and three times daily irrigations for 14 days with alternate irrigant	NOSE score; SNOT-22 score; VAS score; Modified Lund-Kennedy score
Rabago *et al.* [2020]	Randomised control trial (xylitol *vs.* saline *vs.* control)	Patients meeting criteria for Gulf War Illness with moderate to severe chronic rhinosinusitis [40]	Xylitol (1.6% wt/vol); Saline (2% wt/vol)	Irrigation	Twice daily irrigations for 26 weeks	SNOT-22 score; MFI score
Sylvia *et al.* [2020]	Prospective randomised controlled study (xylitol *vs.* saline)	Patients with CRSwNP or CRSsNP refractory to medical treatment [52]	Xylitol (1.6% wt/vol); Saline (0.9% wt//vol)	Irrigation	Three times daily irrigations for 30 days	VAS score; SNOT-22 score; NOSE score

CRS, chronic rhinosinusitis; ESS, endoscopic sinus surgery; SNOT-22, 22-item Sinonasal Outcome Test; VAS, visual analog scale; NO, nitric oxide; iNOS, inducible nitric oxide synthase; NOSE, nasal obstruction symptom evaluation; MFI, multidimensional fatigue inventory; CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis without nasal polyps.

Table 2 Summary of risk of bias assessment in the included trials comparing Xylitol to saline in the treatment of sinonasal disease

Authors [year]	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data
Weissman *et al.* [2011]	Low	Low	Unclear	High	Low	Low	Low
Lin *et al.* [2017]	Low	Low	Unclear	Low	Low	Unclear	Low
Kim *et al.* [2019]	Low	Low	Unclear	Low	Low	Unclear	Low
Rabago *et al.* [2020]	Low	High	Unclear	Low	High	High	Low
Sylvia *et al.* [2020]	Low	Low	Unclear	Low	Low	Low	Low

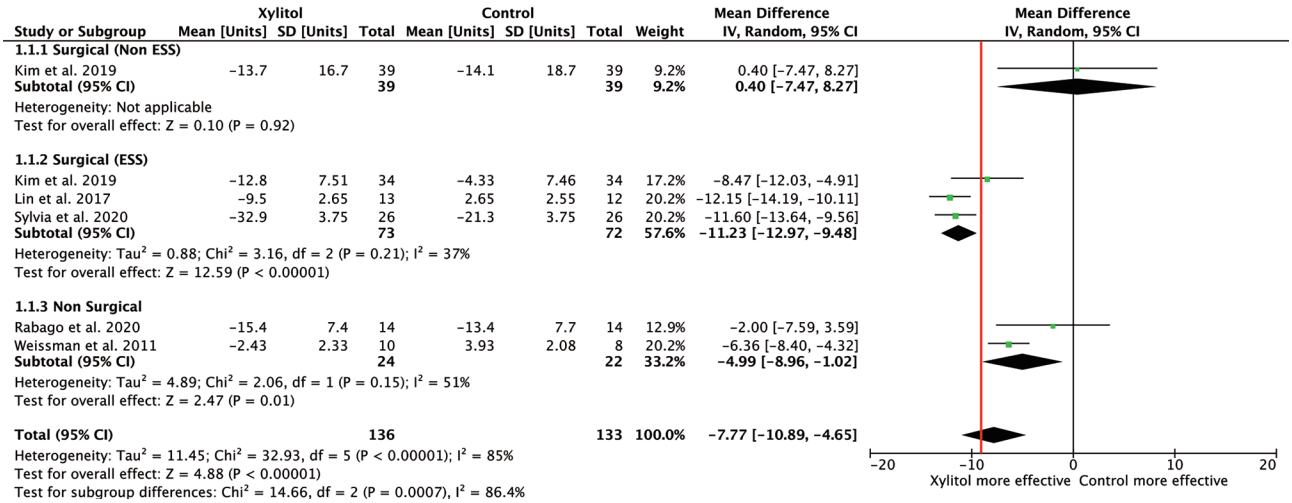

Figure 2 Forest plot summarising the meta-analysis of Xylitol versus saline in the treatment of sinonasal disease

of disease and symptomology in CRS. In comparison to normal saline, xylitol was associated with a greater reduction in SNOT-22 scores (–7.77, 95% CI: –10.89 to –4.65, P<0.00001). In the post-surgical ESS subgroup, the average reduction was greater (–11.23, 95% CI: –12.97 to –9.48, P<0.00001) whilst in the non-surgical subgroup the difference was less noticeable (–4.99, 95% CI: –8.96 to –1.02, P=0.01). In the post-surgical non ESS subgroup there was no reduction in SNOT-22 score with the difference being a positive value of 0.40 (95% CI: –7.47 to 8.27) this result was also not statistically significant. It should however be noted that only one study provided data that was able to be included in the post-surgical non ESS subgroup.

Regarding clinical significance, we compared our SNOT-22 score difference to the predefined MCID score of 8.9. The overall pooled SNOT-22 score and non-surgical subgroup failed to meet this threshold. The post-surgical ESS subgroup met the predefined MCID score, suggesting that xylitol is an effective additive in nasal preparations when given to post-surgical ESS patients with sinonasal disease at reducing overall disease burden as our subgroup analysis demonstrates both a statistically and clinically significant difference when compared to normal saline.

Some patients however, may still report a clinically meaningful change in symptomology despite their SNOT-22 response not exceeding the MCID. Phillips *et al.* examined the MCID for SNOT-22 difference in medically managed CRS patients and determined the score to have high specificity whilst having poor sensitivity (23). This indicates that a considerable number of medically managed CRS patients may experience a clinically significant improvement despite their SNOT-22 response not meeting the predefined MCID threshold. Phillips *et al.* hypothesised that a disproportionate improvement across the SNOT-22 symptom domains could account for the discrepancy. They demonstrated that in a group of patients with a subthreshold MCID score whilst also reporting symptom improvement, the improvement was in the nasal symptom subdomain (15). Relating this back to our analysis, xylitol could also be beneficial in medically managed CRS patients where nasal symptoms are main contributor to their overall symptomology.

Several limitations have been identified in our review. Our meta-analysis was limited by the available literature pertaining to the use of xylitol nasal preparations in sinonasal disease with only 7 small scale RCTs identified prior to assessing for eligibility. Of which 2 unfortunately had to be excluded as they did not include the SNOT-22 score as their outcome measure, preventing a comparable and quantifiable overall assessment of effect. As result we had a total n=191 therefore making our study likely to be influenced by sampling error. It should however be noted that at the time of writing this review, 9 clinical trials looking into xylitol and sinonasal disease are currently registered on the Cochrane Central Register of Controlled Trials.

Significant heterogeneity was present between the included studies, evident in an overall I^2 statistic of 85%, restricting our comparison of studies and thereby increasing the risk of confounding. This is owed to the variable

methodology that exists between the included studies with distinct differences in concentrations of solution, frequency of treatment and study duration. This variability could be explained by the lack of robust evidence at present investigating the use of xylitol in sinonasal disease resulting in a yet to be determined treatment protocol.

A major contributor of bias seen across all included studies was regarding the blinding of participants to their respective intervention or control groups. This was despite measures employed by the investigators such as computer randomisation or providing the solutes in unlabelled packaging. The intervention was a sugar (xylitol) being compared against a salt (saline) and in the context of nasal irrigation, it would be reasonable to expect the participants to be able to taste a difference, therefore introducing an element of blinding error. Weissman *et al.* commented that 21% of their participants mentioned noticing a distinct sugary aftertaste with the xylitol irrigations (24). Hayer *et al.* decided to forego blinding altogether in their trial (19).

Whilst the SNOT-22 score is a well validated outcome measure of sinonasal symptoms, it is a subjective quality of life measure which depends on the patient's specific experience of sinonasal disease. Therefore, the SNOT-22 score can be subject to a certain degree of recall bias, particularly when the scoring system requires the participant to answer 22 questions pertaining to their symptoms. To address this, an objective outcome measure would be required, Cingi *et al.* used rhinomanometry to measure nasal airway resistance pre and post treatment. It was the only reviewed study that incorporated an objective measure and could be considered in future studies as it would reduce recall bias.

To date, there has yet to be a systematic review conducted comparing xylitol against saline as a nasal irrigation solution. Therefore, the results of this review provide a comprehensive summary of the current body of evidence. Where previous trials have reported the SNOT-22 score we compared this against the MCID score to better meaning about the results, thereby allowing the clinician to decide if xylitol would be a suitable treatment of choice for their specific patient.

Conclusions

This review demonstrates that xylitol nasal preparations may be an effective agent of choice for the treatment of sinonasal disease in post-surgical patients who have had ESS as our pooled SNOT-22 mean score difference exceeded the predefined MCID threshold for a clinically meaningful result. The pooled SNOT-22 mean score difference in the non-surgical subgroup failed to exceed the MCID threshold, however xylitol may still be able to achieve a clinically meaningful response in this subgroup if nasal symptoms were the main contributor to their overall symptomology.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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