Effect of Dissolving Xylitol Chewable Tablets versus Xylitol Chewing Gum on Salivary pH and Bacterial Count in Geriatric Bedridden Patients : Randomized Clinical Trial

تأثير أقراص الزيليتول الذائبة و القابلة للمضغ مقارنةً بعلكة الزيليتول على حموضة اللعاب والعد البكتيرى مع مرضى الشيخوخة ملازمى الفراش : تجربة اكلينيكية عشوائية

Proposal

Submitted to conservative dentistry department, Faculty of dentistry, Cairo University, in partial fulfillment of the requirement for PhD degree in Esthetics and Restorative dentistry

By

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I) Administrative information

1) **Title**: " Effect of Dissolving Xylitol Chewable Tablets versus Xylitol Chewing Gum with Geriatric Bedridden Patients on Salivary pH and Bacterial Count in Both Saliva & Interdental Plaque : Randomized Clinical Trial"
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5) **Trial sponsor:** Faculty of Dentistry, Cairo University.
6) **Roles and responsibilities:**

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Bacteriological Assessment:
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Research Ethics Committee (REC) of Faculty of Dentistry, Cairo University; For reviewing protocol of this clinical trial to protect the rights, safety, dignity and well-being of the people participating in the trial.

Research Plan Committee:
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II. INTRODUCTION

1) Background and Rationale:

1.1. Research question:

For the geriatric bedridden patients, will the use of the newly introduced dissolving Xylitol chewable tablets be better in decreasing bacterial count in both saliva and interdental plaque and elevating the salivary pH if compared against xylitol chewing gum?

1.2. Statement of the problem:

Dental caries remains the most prevalent chronic disease in both children and adults, and is one of the most common important global oral health problems in the world, but it is largely preventable ***(Yadav and Prakash, 2016)***. Although caries has significantly decreased over the past four decades, disparities remain among some population groups like geriatric patients and the scenario becomes even more accentuated when it comes to bedridden patients, who are dependent and whose functional capacity is shortened. Moreover, they usually face the given reality that they are constrained to their rooms, without having access to the bathroom which strict their ability for tooth brushing and mouth rinsing ***(Morandi et al, 2018)***.

1.3. Rationale:

So, these bedridden patients who may not have ready access to water are most need of easy swallowing dosage forms like chewable tablets ***(Renu et al,2015)***. Using chewable tablets like the newly introduced "Listerine Ready Tabs" that can be swallowed give them the opportunity to clean their mouth without leaving their beds.

1.4. Review of literature:

During the latter half of the 20th century, the age composition of the population changed dramatically, with more people living to older ages and the older population getting older. This demographic change will have a major impact on the delivery of general and oral health care. ***(Abdul razaq, 2014).*** Improved quality of life at old age will demand tooth retention. However, Retaining teeth disease free and maintaining preventive care for elderly people, is a multi- faceted challenge. ***(Roopa et al, 2011)***

Many elderly persons are hampered in their efforts of performing plaque control procedures by physical disabilities that result in the lack of manual dexterity or impaired range of motion of the wrist, elbow or shoulder ***(Abdul razaq 2014)***.Moreover, the scenario becomes even more accentuated when it comes to bedridden patients as they are constrained to their rooms, without having access to the bathroom which strict their ability for tooth brushing and mouth rinsing. So, such population must take much more interest from us for their oral care.

Xylitol, which presents in our interventions , is a naturally occurring five-carbon sugar polyol .It is a white crystalline carbohydrate known since a century ago. It has been widely studied during the last 40 years for its effect on dental caries. It is found naturally in fruit, vegetables, and berries and is artifacially manufactured from xylan-rich plant materials such as birch and beechwood. ***(Nayak et al, 2014)***

Xylitol reduces the levels of mutans streptococci (MS) in plaque and saliva. It also reduces their acid production potential leading to increase in salivary ph. ***(Nayak et al, 2014)***

It was found that the xylitol bacteriostatic effect on *S. mutans* is by creating a futile cycle that consumes cellular ATP. In a futile cycle, Xylitol is transported across bacterial cell membrane by a phospho-transferase system, generating xylitol-5-phosphate which can not be metabolized and may subsequently be dephosphorylated and exported at the expense of ribitol-5-phosphate . ***(Chen and Wang, 2010)***

Ly et al in 2006 determined the reduction in mutans streptococci levels in plaque and unstimulated saliva to increasing frequency of xylitol gum use at a fixed total daily dose of 10.32 g over five weeks. They randomized participants (n = 132) to either active groups (10.32 g xylitol/day) or a placebo control (9.828 g sorbitol and 0.7 g maltitol/day). All groups chewed 12 pieces/day. The control group chewed 4 times/day and active groups chewed xylitol gum at a frequency of 2 times/day, 3 times/day, or 4 times/day. The 12 gum pieces were evenly divided into the frequency assigned to each group. Plaque and unstimulated saliva samples were taken at baseline and five-weeks and were cultured on modified Mitis Salivarius agar for mutans streptococci enumeration. They found no significant differences in mutans streptococci level among the groups at baseline. At five-weeks, mutans streptococci levels in plaque and unstimulated saliva showed a linear reduction with increasing frequency of xylitol chewing gum use at the constant daily dose. Although the difference observed for the group that chewed xylitol 2 times/day was consistent with the linear model, the difference was not significant. They concluded that there was a linear reduction in mutans streptococci levels in plaque and saliva with increasing frequency of xylitol gum use at a constant daily dose. Reduction at a consumption frequency of 2 times per day was small and consistent with the linear-response line but was not statistically significant.

Milgrom et al in 2006, determined the dose-response of mutans streptococci in plaque and unstimulated saliva to xylitol gum. They randomized participants (n = 132): controls (G1) (sorbitol/maltitol), or combinations giving xylitol 3.44 g/day (G2), 6.88 g/day (G3), or 10.32 g/day (G4). Groups chewed 3 pellets/4 times/d. Samples were taken at baseline, 5 wks, and 6 mos, and were cultured on modified Mitis Salivarius agar for mutans streptococci and on blood agar for total culturable flora. They found that at 5 wks, mutans streptococci levels in plaque were 10x lower than baseline in G3 and G4 (P = 0.007/0.003). There were no differences in saliva. At 6 mos, mutans streptococci in plaque for G3 and G4 remained 10x lower than baseline (P = 0.007/0.04). Saliva for G3 and G4 was lower than baseline by 8 to 9x (P = 0.011/0.038). They concluded that xylitol at 6.44 g/day and 10.32 g/day reduces mutans streptococci in plaque at 5 wks, and in plaque and unstimulated saliva at 6 mos. A plateau effect is suggested between 6.44 g and 10.32 g xylitol/day.

Prathibha et al in 2010 compared the effect of Manuka honey, chlorhexidine gluconate (0.2%) mouthwash and xylitol chewing gum on the dental plaque levels. Sixty healthy male dental students aged between 21 and 25 years (mean age 23.4 years) participated in the study. All the subjects received a professional prophylaxis at the start of the study, with the purpose of making the dentition 100% free of plaque and calculus. The subjects were then randomly divided into three groups, i.e. the Manuka honey group, the chlorhexidine gluconate mouthwash group and the xylitol chewing gum group. Rinsing with water or any other fluid after the procedure was not allowed as also any form of mechanical oral hygiene for all the subjects during the experimental period of 72 h. After the experimental period, the plaque was disclosed using disclosing

solution and their scores were recorded at six sites per tooth using the Quigley and Hein plaque index modified by Turesky-Gilmore-Glickman. They found that the mean plaque scores for Groups I, II and III were 1.37, 1.35 and 1.57, respectively. The ANOVA revealed that between group comparison was significant, with an F-value of 5.99 and a probability value of 0.004. The T-test was carried out to evaluate the inter-group significance, which revealed that the plaque inhibition by Manuka honey was similar to that of chlorhexidine mouthwash. So they concluded that both Manuka honey and chlorhexidine mouthwash reduced plaque formation significantly, better than the xylitol chewing gum.

Kumar, et al in 2013, evaluated the salivary and dental plaque pH changes after consumption of sugared and sugar-free (xylitol) chewing gums in children. They selected a total of 30 school children for this study and divided them into two equal groups and gave both chewing gums for the experiment. They found that children consuming the sugar-free (xylitol) chewing gum showed a marked increase in the pH of saliva and plaque when compared to their counterpart. All these values had a significant difference of $P \leq 0.0001$. So, they concluded that xylitol is a safe natural sweetener which helps to reduce tooth decay. It plays a unique role in preventive strategies for better health.

Nishihara et al in 2014 evaluated the effects of the lactic acid bacterium Lactobacillus salivarius on caries risk factors. They performed their study in 64 healthy volunteers to evaluate the effects of L. salivarius-containing tablets on caries risk factors. They divided participants randomly into four groups, and gave them chewable tablets containing L. salivarius WB21, L. salivarius TI 2711, Ovalgen® DC (antibody against glucosyltransferase from Streptococcus mutans), or

xylitol and then levels of mutans streptococci and lactobacilli, amount of salivary flow, salivary pH, and salivary buffering capacity were assessed before and after taking the tablets. They found that the levels of mutans streptococci seemed to decrease in the L. salivarius WB21, TI 2711, and Ovalgen® DC groups compared to the xylitol group, with no significant differences between the groups. Lactobacilli levels significantly increased in the L. salivarius WB21 and TI 2711 groups compared to the other groups. Concerning salivary flow and salivary pH, they found no significant differences between the groups. Also they found that the salivary buffering capacity significantly increased in the L. salivarius TI 2711 group (P = 0.003) and Ovalgen® DC group (P = 0.002) compared to the xylitol group. And finally they found that, the L. salivarius WB21-containing tablets significantly decreased the number of mutans streptococci (P = 0.039).

Lapiedra et al in 2015, evaluated the effect of a combination saliva substitute for the management of xerostomia and hyposalivation They evaluated the difference between the combination agent of xylitol, beatine and olive oil in a chewable capsule versus the control agent of a sorbitol tablet in subjects with hyposalivation and xerostomia . Their study was 3 weeks in duration, with 2 treatment phases of 1 week and a 7 day wash out period in between. At the end of each treatment phase, subjects returned for a follow up evaluation. At this visit they gave the patients subjective sensation questionnaire, as well as they measured their unstimulated whole salivary flow and stimulated whole salivary flow . They found that there was a greater increase in the unstimulated and stimulated whole salivary flow rate, although the results were not statistically significant. The subjective evaluation as measured by the questionnaire showed that both agents reduced the mean score as

compared to the baseline, although only the findings in the active agent was statistically significant ($p = 0.0015$). They concluded that the active agent provided a significant subjective improvement in speech, swallowing, and decreased subjective xerostomia as compared to the control tablet.

Masoud et al in 2015 evaluated long-term clinical and bacterial effects of using 6 g of xylitol per day for 3 months on patients with full fixed orthodontic appliances. They made a pilot clinical trial that included 41 subjects who were undergoing orthodontic treatment. They divided subjects randomly into three groups. Group A received xylitol chewing gum, group B received xylitol dissolvable chewable tablets, and Group C served as the control group and did not receive xylitol gums or tablets. Clinical examination and the collection of plaque and saliva samples were carried out at baseline and 3, 6, and 12 months. All three groups were given oral hygiene instruction and were put on a 6-month cleaning and topical fluoride schedule. Plaque scores and bacterial counts were used to evaluate the effectiveness of the different approaches at reducing the caries risk. They found that xylitol groups did not experience any more reduction in plaque score, plaque MS counts, or salivary MS counts than the control group nor did they have lower values at any of the time points. They concluded that xylitol does not have a clinical or bacterial benefit in patients with fixed orthodontic appliances. Oral hygiene instructions and 6-month topical fluoride application were effective at reducing plaque scores and bacterial counts in patients with full fixed appliances regardless of whether or not xylitol was used.

Cock et al in 2016 provided a comprehensive overview of published evidence on the impact of erythritol, a noncaloric polyol bulk sweetener, on oral health. *Methods*. A literature review was conducted

regarding the potential effects of erythritol on dental plaque (bioflm), dental caries, and periodontal therapy. The efficacy of erythritol on oral health was compared with xylitol and sorbitol. They found that Erythritol effectively decreased weight of dental plaque and adherence of common streptococcal oral bacteria to tooth surfaces, inhibited growth and activity of associated bacteria like *S. mutans*, decreased expression of bacterial genes involved in sucrose metabolism, reduced the overall number of dental caries, and served as a suitable matrix for subgingival air-polishing to replace traditional root scaling. They concluded that important differences were reported in the effect of individual polyols on oral health with the evidence demonstrating better efficacy of erythritol compared to sorbitol and xylitol to maintain and improve oral health.

Swapnil Oza et al in 2018 determined the effect of chewing gum containing xylitol and sorbitol on mutans streptococci and *Lactobacilli* count in saliva, plaque, and gingival health and compared the efficacy of chewing gums. They designed as a double-blinded randomized uncontrolled clinical trial with two parallel arms. A total of 80 students consented and completed the study. The test group (X) received corresponding pellets with xylitol and the control group (S) was given pellets containing sorbitol and maltitol three times daily for 30 days. Clinical scoring and saliva samples were collected at three different intervals, at baseline, 15^{th}, and 30^{th} day of the study. The outcome measure was plaque index score, gingival index score, salivary mutans streptococci, and *Lactobacilli* counts. They found that there was no statistically significant difference between the mean of mutans streptococci count of test and control group at baseline and 15^{th} day, but there was statistically highly significant difference ($P = 0.00$) between the mean of mutans streptococci count in test and control group on the 30^{th}

day. The mean of *Lactobacilli* count, plaque index, and gingival index score between test and control group showed no statistically significant difference at baseline, 15th day, and 30th day. The results suggest that only xylitol gum may interfere with the mutans streptococci composition and reduce it after continuous use of 30 days effectively as compared to sorbitol gum, but both the gums are equally effective on salivary *Lactobacilli*, plaque, and gingiva at different intervals.

Rafeek et al in 2019, conducted a study to see if chewing gum containing xylitol may help prevent caries by reducing levels of mutans streptococci (MS) and lactobacilli in saliva and plaque. In this study, they employed high-throughput sequencing of the 16S rRNA gene to profile microbial communities of saliva and plaque following short-term consumption of xylitol and sorbitol containing chewing gum. Participants (n = 30) underwent a washout period and were randomly assigned to one of two groups. Each group chewed either xylitol or sorbitol gum for three weeks, before undergoing a second four-week washout period after which they switched to the alternate gum for three weeks. Upon analysis of samples collected before and after each intervention, they identified distinct plaque and saliva microbial communities that altered dependent on the order in which gum treatments were given.They found that neither the xylitol nor sorbitol treatments significantly affected the bacterial composition of plaque. Lactobacilli were undetected and the number of Streptococcus mutans sequence reads was very low and unaffected by either xylitol or sorbitol. However, sorbitol affected several other streptococcal species in saliva including increasing the abundance of S. cristatus, an oral commensal shown to inhibit bacteria associated with chronic periodontitis.

1.5. Choice of comparator:

In our study , the comparator is xylitol chewing gum as ***Nayak et al in 2014*** mentioned that the predominant modality for xylitol delivery has been chewing gum, as moreover the antibacterial effect of xylitol , chewing a gum accelerates the processes of rinsing away acid by stimulating salivary flow and uptake of benefacial calcium phosphate molecules to remineralize tooth enamel. ***(Chen and Wang, 2010)***

And another special cause in this study is our population who are geriatric bedridden patients. As chewing a soft gum is a simple, easy, convenient independent procedure that don't need any physical effort or caregiver and also don't need from them to leave their beds or to go to the bathroom like for brushing or rinsing.

2) Objectives:

2.1. Aim of the study:

This study will be conducted to evaluate the effectiveness of using dissolving Xylitol chewable tablets versus xylitol chewing gum with bedridden geriatric patients ,as an alternative to tooth brushing and mouth rinsing, in increasing salivary pH and decreasing bacterial count in both saliva and interdental plaque.

2.2. Hypothesis:

The null hypothesis is that the newly introduced dissolving xylitol chewable tablets have the same effect as xylitol chewing gum on salivary pH and bacterial count in both saliva and interdental plaque when used with geriatric bedridden patients.

2.3. Primary and secondary objectives:

PICOTS

P (problem /population): geriatric bedridden patients

I (intervention /indicator): dissolving Xylitol chewable tablets **"listerene ready tabs"**

C (control /comparator): xylitol chewing gum **"Trident original"**

O (outcome) :

O1: salivary streptococcus mutans count

O2**:** interdental plaque bacterial count

O3: salivary pH

Type	*Outcome Name*	*Measuring Device*	*Measuring Unit*
1ry	**Salivary S.mutans count**	**Bacterial Culture**	**CFU/ml**
2ry	**Interdental plaque Bacterial count**	**Bacterial Culture**	**CFU/ml**
3ry	**Salivary pH**	**pH Meter**	**Moles per litre**

T (time):

T0: Baseline

T1: 5 minutes

T2: 15 days

S (study): randomized clinical trial.

2) Trial design:

Randomized clinical Trial, parallel arms.
Trial framework: Equivalence frame
Allocation ratio: 1:1.

III. METHODS

A) Participants, interventions, & outcomes

1) Study Settings:

This clinical trial will be held in the Faculty of medicine, Cairo University, Egypt.

2) Eligibility criteria:

a- Eligibility criteria of participants :

- **Inclusion Criteria :**

(1) Age range above 65 years old
(2) Bedridden patients
(3) Males or females
(4) Concious patients
(5) Co-operative patients approving to participate in the trial.
(6) Subjects who signed informed consent

- **Exclusion criteria:**

(1) Individuals had taken antibiotics during the last four weeks or anticipated doing so during the study
(2) Subjects who wore removable prosthesis
(3) Patients with systemic diseases that have any oral manifestations
(4) History of Smoking
(5) Allergy to any of chewing gum or tablets ingredients
(6) Evidence of tempromandibular joint disorders
(7) Presence of intraoral infections
(8) Currently using any mouth rinse

b- Assessors and operator criteria:

Operator: M.A. (Master degree),

Assessors: H.M. (Master degree), E.M. (Master degree).

3) Interventions:

In our study, we selected for both intervention and comparator, materials that don't need from those geriatric bedridden patients to leave their beds with both materials are xylitol containing materials but with different delivery system. The intervention is dissolving xylitol chewable tablets and the comparator is xylitol chewing gum.

The intervention is the newly introduced dissolving xylitol chewable tablets " Listerine Ready Tabs " .Technically, it's a rectangular-shaped, bilayer-compressed tablet that once chewed, creates just enough liquid to swish around your mouth to get a whole-mouth clean feeling. As manufacture claimed the tablet is easy to use just in three simple steps: chew (to activate), swish (to clean), then swallow as unlike mouthwashes which may contain alcohol and other ingredients not intended for ingestion, Listerine Ready Tabs are alcohol-free and safe to swallow which is highly suitable for bedridden patients. It's composed of Xylitol, Erythritol, Isomalt, Calcium Carbonate, Flavor, Magnesium Stearate, Cellulose Gum, Hydroxypropyl Cellulose, Tetrasodium Pyrophosphate, PVP, Sucralose, Acacia Senegal Gum, Potassium Acesulfame, Glycerin, and Potassium Sorbate. Moreover the beneficial effect of xylitol ,as mentioned before, the addition of Erythritol in its composition adds more value for the tablets as all studies strongly support the idea of erythritol as a caries-reducing dietary polyol with inhibitory effect on the growth of certain mutans streptococci isolates by a mechanism of growth inhibition differs from that caused by xylitol. Morover, combinations of erythritol and xylitol will turn out to exert promising caries-limiting effects in humans as the combined effects may exceed or at least equal the separate effects of both polyols. ***(Makinen, 2010)***

The comparator is Original Trident which is a soft gum sweetened with xylitol . It also contains sorbitol, Mannitol, Aspartame, Sucralose and Acesulfame potassium.

For our methodology, the saliva and the dental plaque samples will be collected along the previously determined timeline; **T0:** before taking either the intervention or the comparator and **T1:** immediately after 5min and **T2:** 15days (for salivary ph measurement and bacterial count in both saliva and interdental plaque).

- **For Intervention group**:

Participants had to take one tablet three times per day, taken orally, after eating. Participants will be directed to chew the tablet (to activate), swish (to clean), then swallow it . They were not to take other probiotic products or mouth rinse throughout the study period. Neither professional prophylaxis nor tooth brushing instruction will be performed before or during the experimental period. ***(Nishihara et al, 2014)***

- **For Comparator group:**

Participants were instructed to chew the gum three times daily after eating for 5 min ***(Swapnil et al, 2018***).Also ,like the intervention group, they were not to take other probiotic products or mouth rinse throughout the study period and neither professional prophylaxis nor tooth brushing instruction will be performed .***(Nishihara et al 2014)***.

- **Salivary sampling:**

On the day of saliva collection, subjects were instructed not to eat or drink anything for at least 1 hour before the collection of saliva sample. The participants were asked to rinse their mouth with water before

collection of saliva to avoid the contamination of food debris. Then, subjects were instructed to let saliva collect without swallowing for at least 1 min, and then to expectorate into sterile graduated collection tube with the help of a sterile funnel. The collected saliva will be divided into two parts : first; at least 2 ml for ph measurement and second; the remaining salivary sample was transferred into 5-ml sterile disposable vials and carried in a vaccine carrier with freezing mixture to the laboratory, where analysis of the sample was done on the same day. ***(Swapnil et al, 2018***)

- **Plaque Sampling:**

Interdental plaque samples were collected from mesial and distal surfaces with the help of a sterile spoon excavator. These plaque samples were then dispersed in a test tube containing double de-ionized distilled water. ***(Kumar et al 2013***)

- **Salivary ph measurement:**

The pH values were assessed with the help of a pH meter . The required minimum volume of saliva is 2 ml in a sterile test tube so that the bulb of the measuring electrode could dip sufficiently into the saliva samples. Then, collected samples will be then subjected for the pH measurements. ***(Kumar et al 2013***)

- **Culture of mutans streptococci:**

The saliva and plaque sample was homogenized by shaking in a vortex for 30 s to disperse bacterial aggregates. Hundred microliter of saliva and plaque were diluted with 1 ml of sterile peptone water to obtain 1:10 dilution of both saliva and plaque. About 100 µl of the diluted saliva and plaque was further added to 1 ml of sterile peptone water to obtain a

dilution of 1:100. This procedure was repeated to obtain a dilution of 1:1000. This dilution was used for microbial analysis. *S. mutans* will be cultured on mitis salivarius-bacitracin (MSB) agar. The media will be prepared according to the manufacturer's instructions and poured into sterile disposable microbial culture plates and refrigerated till inoculation is done. Under strict aseptic conditions , 5 µl aliquots of each dilution will spread using micropipette onto MSB solid media and sterile glass rod will be used to give homogenous bacterial growth. The MSB agar plate will be incubated for 48 h at 37°C, anaerobically in an atmosphere of 5% CO2 using candle jar. After 48 h of incubation period, *S. mutans* will appear on the culture plate as small, rough, raised, and adherent colonies. Colonies so identified will be counted by a single examiner, who will be unaware of the treatment of the patients. ***(Swapnil et al, 2018***)

1) Outcomes: (*Table 1*)

<table>
<tr><th>No.</th><th>Outcome Name</th><th>score</th><th>Criteria</th><th>type</th><th>Methods of aggregation</th></tr>
<tr><td rowspan="2">1ry</td><td rowspan="2">Salivary S.mutans count</td><td rowspan="2">VL: very low
L: low
M:Moderate
H:High</td><td rowspan="2">10^2 cfu/ml
10^3 cfu/ml
10^4 cfu/ml
10^5 cfu/ml</td><td rowspan="3">Categorical ordinal</td><td rowspan="3">Absolute risk will be reported for each intervention independently. Relative risk will be used to compare both interventions with 95 % CI.</td></tr>
<tr><td>2ry</td><td>Interdental plaque Bacterial count</td></tr>
<tr><td colspan="2">Swapnil et al, 2018</td></tr>
<tr><td rowspan="2">3ry</td><td rowspan="2">Salivary ph</td><td>Numerical values</td><td>Normal salivary ph = 6.2 - 7.6</td><td rowspan="2">Continous</td><td rowspan="2">Mean and Standard deviation</td></tr>
<tr><td colspan="2">Baliga et al,2013</td></tr>
</table>

2) Participant timeline: *(Table 2)*

Activity	Staff member	T0 Baseline	T1 After 5 min	T2 After 15 days
Recruitment	***Y.S.***	***X***		
Diagnosis	***Y.S.***	***X***		
Consent	***Y.S.***	***X***		
Baseline data collection	***Y.S.***	***X***		
Randomization	***Y.S.***	***X***		
Saliva & Plaque sampling	***M.A.***	***X***	***X***	***X***
Outcome assessment	***H.M.*** ***E.M.***	***X***	***X***	***X***

3) Sample size calculation:

A power analysis was designed to have adequate power to apply statistical test of the research hypothesis that dissolving xylitol chewing tablets will have the better antibacterial effect than xylitol chewing gum against mutans streptococci after 1 month. According to the results of ***Swapnil et al. in 2018*** in which the probability of bacterial count reduction to 10^2 for xylitol chewing gum (comparator) was (0.15), probability of bacterial count reduction to 10^3 was (0.6) and probability of bacterial count reduction to 10^4 was (0.25) with effect size w=0.578 (n=29). If the estimated probability of dissolving xylitol chewing tablets for bacterial count reduction to 10^2 is (0.35), probability of bacterial count reduction to 10^3 is (0.5) and probability of bacterial count

reduction to 10^4 was (0.15) with effect size w= 0.43 (n=53). By adopting an alpha (α) level of 0.05 (5%), power=80%. The predicted sample size (n) was a total of (82). Sample size was increased by (20%) to account for possible dropouts during follow-up intervals to be total of (98) cases i.e. (49) for each group. Sample size calculation was performed using G*Power 3.1.9.2.

4) Recruitment:

Patients will be recruited by Y.S from intensive care units in kasr el Ainy hospitals, Faculty of Medicine, Cairo University, where there is a continuous and high patient flow from which eligible patients will be recruited to fulfill the eligibility criteria .

B) Assignment of interventions (Allocation):

1) Sequence generation:

Simple randomization will be done by generating numbers from 1:98 using Random Sequence Generator, Randomness and Integrity Services Ltd (https://www.**random**.org/) by Y.S. Each generated random number will represent assigning intervention and comparator in a random manner, i.e.: No. 1 intervention No.2 comparator.

2) Allocation concealment:

Operator M.A. will choose between numbers in an opaque sealed envelope, which will be arranged by Y.S. who will not be involved in any of the phases of the clinical trial. Data will be recorded on a computer by M.A. and H.M. and all records of all patients will be kept with the main supervisor A.E.

3) Implementation:

Y.S. will generate the allocation sequence, enroll participants ,and assign participants to interventions.

4) Blinding:

The operator will be blinded to material and assessors H.M. & E.M. will be blinded to the material assignment.

C) Data collection, management, and analysis:

1) Data collection methods:

1.1. Baseline data collection:

For every patient medical and dental history will be taken. Examination charts will be filled by Y.S.

1.2. Outcome data collection:

Outcomes will be evaluated by two assessors H.M. & E.M. before interventions, after 5 minutes and 15 days, if both assessors differ in score, they will discuss, if did not agree a third assessor will resolve the conflict.

1.3. Patient retention:

The phone number of the patient or his/her caregiver will be recorded in the patient's chart. The patient will receive a phone call by Y.S. to remind him of the time of the operator M.A. visit for saliva and plaque sampling. Moreover, patients will receive a daily phone message in the time assigned for chewing either the gum or the tablet.

2) Data management:

Data entry will be accomplished by M.A. & revised by E.M. All data will be stored on computer and will be encrypted using a password. This is

done to allow accurate data entry thorough revision and protect data from being inadvertently used. Data will be backed up on another computer to prevent it from being lost.

3) Statistical methods:

Data will be analyzed using IBM SPSS advanced statistics (Statistical Package for Social Sciences), version 25 (SPSS Inc., Chicago, IL). Categorical data will be described as absolute risk for each intervention independently and relative risk when comparing both interventions. Comparisons between categorical variables will be performed using the chi square test and Kruskal Wallis will be used to test interaction of variables. Continuous data will be described using mean and standard deviation. Comparison between continuous data will be performed using t-test and two-way ANOVA will be used to test interaction of variables. A p-value less than or equal to 0.05 will be considered statistically significant and all tests will be two tailed.

D) Monitoring:

1) Data monitoring:

The main supervisor (A.E.) will monitor this study. His role is to monitor any risk of bias from participants, operator or assessors, monitor blinding of the assessors and monitor patient safety, outstanding benefits or harms.

2) Harms:

No Harms are expected. But if any adverse effect occurs then the senior supervisor has the right to call for stopping the trial if more than 30% of cases showed any harms or side effects.

3)Auditing:

In this trial auditing will be done by the main and co-supervisors (A.E., A.H. & O.S.) to assure quality of the research methods, sampling techniques and interventions.

IV) ETHICS AND DISSEMINATION:

1) Research ethics approval:

Application forms for accomplishing clinical trial, checklist and informed consent of Research Ethics Committee (REC) Faculty of Oral and Dental Medicine, Cairo University will be retrieved and filled, then will be delivered for REC committee for approval, this is done to prevent any ethical problems during the study or any harms for any of the participants.

2) Protocol amendments:

If a new protocol will be used a protocol amendment will be submitted, containing a copy of the new protocol and a brief explanation about the differences between it and the previous protocols. If there is a change in the existing protocol that affect safety of subjects, investigation scope, or scientific quality of the trial an amendment containing a brief explanation about the change must be submitted. If a new author will be added to accomplish the study an amendment including the investigator's data and qualifications to conduct the investigation will be submitted to prevent ghost authorship.

3) Consent or assent:

Y.S. is responsible of admitting and signing the informed consents during enrollment day.

4) Confidentiality:

The name and the personal data of the participants will not appear on the protocol form and should be maintained secured for 10 years after the trial. This is done for protection of participants' privacy and civil rights.

4) Declaration of interests:

There is no conflict of interest, no funding or material supplying from any parties.

5) Access to data:

Access to final data will be allowed to M.A. and the main and co-supervisors (A.E., A.H. & O.S.) who are not involved in assessment of the outcome.

6) Ancillary and post-trial care:

Patients will be followed up after the end of the study period to ensure oral hygiene measures.

7) Dissemination policy:

- Full protocol will be published online in https://clinicaltrials.gov/ to avoid repetition, and keep the integrity of the research work.
- Thesis will be discussed in front of a judgment committee.
- The study will be published to report the results of the clinical trial.

V) APPENDICES:

Informed Consent Model of (REC) Faculty of Dentistry, Cairo University will be used in this study.

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