

Study title: Effectiveness of using silver diammine fluoride solution and combination of povidone iodine and sodium fluoride varnish in preventing dental root caries in elders: a randomized, double-blind, non-inferiority trial

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Summary

Dental caries (tooth decay) is common among elders in Hong Kong and worldwide, placing heavy burden on the dental care services. There is an urgent need to develop effective and practical management approaches to improve the dental caries situation in the elders, especially among those living in residential care homes whose dental caries status is amongst the worst. The main objective of this study is to compare the effectiveness and cost-effectiveness of 4-monthly application of 10% povidone iodine solution followed by 5% sodium fluoride varnish with those of annual application of 38% silver diammine fluoride solution on the prevention of new dental root caries in elders. A secondary objective is to compare the effectiveness of the two interventions mentioned above on arresting (halting the progression) active root surface caries in the elders, thus avoiding the need for placing dental restorations.

This proposed study is a randomized double-blind controlled clinical trial with 24-month follow-up. A total of 332 elders aged 60 years or above living in residential homes or attending long-term care facilities in different districts in Hong Kong will be recruited. This sample size is sufficient for appropriate statistical analysis of non-inferiority with power set at 90% and allowing for a 20% dropout. Baseline clinical examination will be conducted by a single calibrated examiner in the homes using an intra-oral LED light, dental mirrors and probes. Subjects will be randomly allocated to one of the two study groups: 1) positive control - receive annual application of 38% silver diammine fluoride solution; and 2) test - receive application of 10% povidone iodine solution followed by application of 5% sodium fluoride varnish every 4 months. Follow-up examinations will be carried out after 12 and 24 months by the same blinded examiner to assess the clinical outcomes, i.e. whether new dental caries has developed and whether the active root surface caries lesions found at baseline have become arrested (hardened). Results of this study will provide the much needed evidence to guide the dental professionals in Hong Kong and worldwide in deciding on the most appropriate intervention for the prevention and management of dental caries in the older adults, especially those living in institutions.

1. Background

With ageing of the population in most of the economically well-developed areas, tooth decay in the elders has become an important dental public health issue and a heavy burden on the oral health care system. The latest Hong Kong territory-wide oral health survey conducted by the government in 2011 found that 48% of the 65-74 year-old community-dwelling elders had untreated dental caries and 25% of them had root surface caries (Department of Health, 2013). Furthermore, the same survey found that the dental caries situation of the elders who lived in residential care homes or attended long-term care facilities was worse. The institutionalized elders are a high risk group for dental caries in Hong Kong as well as in other countries (Chalmers et al., 2002).

Untreated tooth decay can lead to pain and loss of teeth, and affect general health. Thus, there is an urgent need to develop effective preventive and management measures to improve the dental caries situation among the elders, especially those living in residential care homes. The Hong Kong government financially support non-profit-making non-governmental organizations (NGO) to establish dental outreach teams to provide on-site basic dental care services to the elders who are receiving long-term care. At present, there are around 20 NGO dental outreach teams serving over 30,000 elders in most of the residential care homes throughout Hong Kong. The dental outreach teams, consisting of dentists and dental assistants, bring along hand instruments and portable dental equipment to the residential homes and provide on-site dental examination, oral health education, prevention, scaling and simple dental restorations (Lo et al., 2004). The services of the outreach dental teams follow a general protocol, and are coordinated and monitored by the government Department of Health.

In a recent systematic review by Gluzman and co-workers (2013), eight preventive agents for preventing dental root caries in older adults were identified. In the conclusion, they recommended that the best choice for primary prevention of root caries was annual application of 38% SDF solution while that for secondary prevention of root caries, i.e. arresting active lesions, was professional application of 5% NaF varnish every 3 months.

In a randomized clinical trial with 3-year follow-up conducted among 306 elders living in 21 residential homes in Hong Kong (Tan et al., 2010), it was found that compared to the controls who only received regular oral hygiene instructions, annual topical application of 38% SDF solution could reduce development of new root caries by 71%. The same study also found that application of 5% NaF varnish every 3 months could prevent root caries as well but the prevented fractions were lower than that of SDF solution. It was also found that presence of visible plaque on root surface was a significant risk factor for dental caries, highlighting the need for good plaque control (Tan & Lo, 2014).

Povidone iodine is a newer antiseptic agent for dental use with clinical evidence showing that it is able to inhibit the activities of acidogenic bacteria including (Evans et al., 2015). In a controlled clinical trial on 30 children with severe early childhood caries, it was found that application of 10% povidone iodine every 3 months significantly reduced the amount of *Streptococcus mutans* and caries development over the 12-month study period (Simratvir et al., 2010). Whether the caries prevention effect of fluoride varnish can be enhanced by regular use of an effective anti-plaque agent such as povidone iodine needs to be assessed by conducting randomized clinical trials.

2. Objectives of the study

1. The primary objective is to compare the effectiveness and cost-effectiveness of 4-monthly application of 10% povidone iodine solution followed by 5% NaF varnish with those of annual application of 38% SDF solution, used as a positive control, in preventing new dental root caries in elders who live in residential homes or attend long-term care facilities..
2. The secondary objective is to compare the effectiveness and cost-effectiveness of the above two methods in arresting active root surface caries among these elders.

Null hypotheses to be tested:

1. In this non-inferiority randomised controlled trial, the primary hypothesis to be tested is that 4-monthly application of 10% povidone iodine solution and 5% sodium fluoride varnish is at least not appreciably worse than a 38% SDF solution in preventing new dental root caries development over a 24-month period. The primary outcome measure is the development of new root surface caries lesions in the teeth of the elders.
2. The secondary hypothesis to be tested is that 4-monthly application of 10% povidone iodine solution and 5% sodium fluoride varnish is at least not appreciably worse than a 38% SDF solution in arresting active root caries over a 24-month period. The secondary outcome measure is the conversion of active (soft/demineralized) root surface caries lesions to inactive (hard/remineralized) lesions.

3. Methods and Materials

3.1. Study population

The study population of this proposed clinical trial is adults aged 60 years and above living in residential care homes or attending long-term care facilities in Hong Kong. The subject inclusion criteria are:

1. have at least 6 teeth which are not indicated for extraction, and
2. have basic self-care ability.

Adults with one or more of the following conditions will be excluded:

1. have serious debilitating health/medical conditions, and
2. have cognitive problems or major problems in communication.

About 10 residential care homes or long-term care institutions served by NGO dental outreach teams in various districts with different background, such as private or publicly funded homes, will be selected by the PI in consultation with the NGOs. All elders living in the selected residential homes will be invited to attend a free dental examination. Elders fulfilling the inclusion criteria will be invited to participate in this study and informed written consent will be obtained before commencement of the study. Dental treatments other than the study interventions will be provided by dentists from the NGOs which serve the residential homes.

3.2. Sample size

This non-inferiority trial aims to compare the caries preventive effect of applications of 38% SDF solution and that of combined 10% povidone iodine solution and 5% NaF varnish. A non-inferiority margin of 0.8 surface for the difference in the mean number of new caries surfaces over the 24-month study period is considered not clinically significant. The estimated sample size is based on the lower limit of the 2-sided 95% confidence interval for the difference set above the non-inferiority margin and the statistical power of the study being set at 90% ($\beta=0.10$). The estimated standard deviation is 2.0, based on the results of a previous clinical trial conducted in Hong Kong (Tan et al., 2010). Using the statistical power analyses software, G*Power (version 3.1.7; Franz Faul, Universität Kiel, Kiel, Germany), the total required number of elders in each group is calculated to be 133. Allowing for a drop-out rate of 20% in this 24-month study, an initial sample size of 166 subjects in each group or a total of 332 subjects is needed.

With a total sample size of 332 subjects and an estimated mean number of one untreated early/shallow root caries lesions per subject (Department of Health, 2013), there will be 332 root caries lesions in total or 166 lesions in each study group for caries arrest treatment. With this sample size, there is approximately 85% power that an absolute 15% difference in dental caries arrest rates between two groups can be shown to be statistically significant at the 5% level using Chi-square test when the overall success rate of the caries arrest treatment is around 80%.

3.3. The baseline and follow-up examinations

The baseline and follow-up examinations after 12 and 24 months will be carried out in the residential home by a single trained examiner. A portable dental chair, an intra-oral LED light, disposable dental mirrors and CPI probes will be used in the examination.

For each tooth that is not indicated for extraction, status of its crown and its root will be assessed and recorded separately. Caries diagnosis is based on visual and tactile inspection. No radiograph will be taken. Plaque and food debris that obscures visual inspection of the tooth surfaces will be removed. Four surfaces (mesial distal, buccal and lingual) per tooth will be examined and the status will be recorded using the following codes which basically follow the criteria recommended by the International Caries Detection and Assessment System (ICDAS II) Coordinating Committee (2009).

The oral hygiene status of the subject will be assessed and recorded by using the Visible Plaque Index (Ainamo & Bay, 1975). The presence or absence of visible plaque will be recorded on four surfaces (mesial, distal, buccal and lingual) per tooth.

The gingival status of the subject will be assessed and recorded using by the Gingival Bleeding Index (Ainamo & Bay, 1975). The presence or absence of bleeding within 10 seconds after running a probe across the gingival margin will be recorded on four surfaces (mesial, distal, buccal and lingual) per tooth.

Other information that will be recorded included whether the subject normally wears a removable partial denture or not, and the subject's general health status and medications that affect saliva flow rate.

The same examiner will carry out all the baseline and follow-up examinations without knowing the study group assignment of the subjects. It has been shown that good intra-examiner reproducibility can be achieved after training (Tan et al., 2010) and a random sample of 10% of the subjects will be re-examined during each examination to monitor intra-examiner reproducibility.

At the examinations, the subjects will be asked to report on their oral hygiene practices, use of fluoridated toothpaste and other topical fluoride agents, and use of dental services during the study period.

3.4. Interventions

Oral health education talk and instructions on how to keep good oral hygiene will be provided at baseline and every year to all the elders in the selected residential homes. Standard fluoride toothpaste with 1000-1500 ppm fluoride will be provided free to all the elders in the selected residential homes over the 24-month study period.

After the baseline examination, subjects satisfying the inclusion criteria of the study will be stratified into two groups according to the number of natural teeth in their mouth, those with 12 or fewer teeth and those with 13 or more teeth. The subjects will then be assigned to one of the two study groups by a research assistant using a block randomization method with a block size of 6. The stratified randomization procedure will help to ensure that

the numbers of teeth involved in the two study groups are balanced. The group assignment of the study subjects will be concealed and placed in a sealed envelope, and will not be made known to the examiner who evaluate the study outcomes.

The interventions for the two study groups will be provided by other dentists and are described below:

Group 1 – plaque on the root surfaces of all teeth in the subject’s mouth will be removed by a small brush and a 38% SDF solution (Saforide, Toyo Chemical, Japan) will be applied onto the root surfaces using a microbrush/applicator. This will be repeated every year.

Group 2 – plaque on the root surfaces of all teeth in the subject’s mouth will be removed by a small brush and a 10% povidone iodine solution (Betadine, Mundipharma, Switzerland) will be applied, then followed by application of a 5% sodium fluoride varnish (Duraflor, Medicom, Canada) using a microbrush/applicator. This will be repeated every 4 months.

3.5. Statistical analysis

The collected data will be entered into a computer and analyzed using the software SPSS for Windows version 20. T-test and Chi-square test will be used, as appropriate, to assess the differences in the distribution of age, gender, denture wearing, number of remaining teeth, number of active caries lesions, oral hygiene practice and status, and gingival status at baseline between the two study groups.

The number of root surfaces with new caries found at each follow-up examination will be calculated. Two-sample t-test test will be used to find out if there are statistically significant differences between the two study groups in the number of tooth surfaces that have developed new dental caries. Both intention-to-treat and per protocol analysis will be performed to compare the effectiveness and efficacy of the two study preventive methods.

Two-level, tooth surface and subject, survival analysis will be used to assess the rates of arrest of active root surface caries in the two study groups (Wong et al. 2005). The statistical significance level for all tests will be set at 5%.

4. References

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