‘COMPARISON OF TWO FLUORIDE APPLICATION REGIME IN ORAL CANCER PATIENTS. A RANDOMIZED CONTROLLED TRIAL’.

SYNOPSIS SUBMITTED

by

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For Ph.D. Degree in Faculty of **ONCOLOGICAL SCIENCES**

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DECLARATION

I hereby declare that the synopsis entitled **"COMPARISON OF TWO FLUORIDE APPLICATION REGIME IN ORAL CANCER PATIENTS; A RANDOMIZED CONTROLLED TRIAL. "** is my own original work and it has not formed the basis for the award of any degree, diploma, associateship or fellowship of similar other titles.

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1. Background and Objective

Oral cancer is one of the among the most common cancers in Indian population. According to GLOBACON 2018, India has 11.4 % incidence of oral cancer being the most common cancer among males and fourth most common cancer in females. More than one lakh individuals were diagnosed with oral cancer in India in 2018. [1] Treatment of oral cancer primarily includes surgery, radiotherapy and chemotherapy, either as a single modality or in combination of the above. The supportive treatments are rarely addressed due to constraints of economics and lack of integrated supportive care as part of the standard cancer treatment protocol.

Supportive care for oral cancer includes rehabilitation and restoration of dental health of the patient. This includes making the patient achieve effective mastication, swallowing, speech and oral and facial esthetics in an optimal manner. This is the standard of care in western population, but in India supportive care is introduced only when the known side effects of cancer treatment are presented. This results in a very poor quality of life in these patients, even when their cancer is cured.

India is both the highest consumer and producer of tobacco in the world and hence contributes to largest number of newly diagnosed cases of oral cancer annually. Indian population also has very poor oral health indicators compared to western population. It has been established as a fact that Tobacco is a common causative agent and risk factor for both poor oral health and oral cancer.[2] To make matter worse if the population with very poor oral health also has a high incidence of tobacco use, the transition of oral premalignant lesion into cancer occurs at a faster rate. Tezal et al. in their work have reported periodontitis as a risk of developing oral and oropharyngeal cancer.[3-5] These conditions predispose our population to be at a very high risk of oral cancer.

There are various reasons for suboptimal to poor oral care among Indian population, especially those diagnosed with oral cancer.. The main reason is the lack of awareness in oral health and limited government aids for National oral health program.

Quality of life is now becoming the bench mark of treatment evaluation apart from being one of the goals of treatment. Only a disease-free survival isn't considered as a valid success of treatment anymore. Rather a disease free survival with good quality of life is becoming the goal of treatment in these times of patient-centric holistic care. Now in context of cancer care and treatment, 'It is the time of not just adding years in life, but adding life in the years'. Inclusion of oral supportive care increases quality of life in oral cancer patients. [6-8]

Majority of our patients do not get preventive and supportive oral care form the time of diagnosis of cancer and thereafter as a part of routine protocol in most of

the cancer centers across the country. This is because of lack of integration of dental experts in decision making and as part of the supportive care team of the oncology unit. Very few centers in India have a dental expert as an active part of the oncology cancer care team for supportive and preventive needs of the patients. Patients are also not aware of the oral health supportive care needs during the cancer treatment unless the complications arise after the treatment of cancer.

To the best of our knowledge there are no national guidelines in India, as of now on the standard oral care protocol to be followed by the oncology professionals in supportive care of every head and neck cancer patients. Based upon our experience and training we need to develop an institutional oral care protocol for resource limited setting like ours, which we are providing in our center since the last few years. Introduction of this protocol, namely 'Oral care module' has reduced many oral and dental complications such as osteoradionecrosis of jaw, radiation caries and oral functional efficiency which arise as the side effects of cancer treatment affecting quality of life of our patients. We aim to validate our oral care protocol and document it as a standard of oral care for cancer patients in the economically restricted environment such as ours.

Use of fluoride is well established in prevention of dental decay, as well as the fact that a specific type of dental decay known as radiation caries is the hallmark of oral cancer patients who receive radiation as part of cancer treatment.[9] Chemotherapy and surgery lead to xerostomia resulting in tooth decay. All these patients are classified as high risk for caries due to altered quantity of saliva. American Dental Association with their paper landmark on clinical recommendation for the use of topical fluoride

have classified patients with xerostomia in the high risk category. [10] These recommendations were made keeping in mind the children with risk of caries, specific needs of oncology patients were not assessed in depth. We hence aim to assess needs of professional topical fluoride specific to patients receiving radiotherapy.

Tooth decay starts at faster rate in matters of weeks and hence an effective plan is essential to address this known problem. As a part of our oral care module we provide professional fluoride application before cancer treatment and then on 4 monthly basis for first year after cancer treatment and then 3-6 monthly for lifelong according to National Comprehensive Cancer Network; NCCN 2018 guidelines.[11] British Society For Disability & Oral Health; BSDH 2018 guidelines also suggest similar recommendations along with home application of home fluoride gel lifelong and daily flossing and use of fluoride toothpaste.[12]

Fluoride is recommended for its protective use as both professional and home application. [13] The mode, duration and frequency of use is variable in literature with very less available data on specific treatment needs for oral cancer patients. To explore such requirement in oral cancer patients, we would like to observe the needs of oral cancer patients for fluoride use and compare the type and frequency of fluoride use.

Landmark studied in 1940s on topical use of fluoride gel and varnishe have been conducted by Bibby et al and Knutson et al. They reported caries reduction ranging from 30 to 40 percentage from use of topical fluoride.[13-15]These studies made framework for recommendation for fluoride in children. Based on these results projections were made regarding fluoride recommendations for adult population. There are very few randomized studies on fluoride use in cancer patients, Horiot et al

in there landmark randomized trial on dental preservation compared fluoride gel and fluoride dentifrice and recommended daily use of fluoride gel over fluorinated dentifrice for home use.[16]

Daly et al and Drezein et al recommended use of sodium fluoride gel daily home application in patients who have received radiation treatment and reported improved outcomes in term of decay.[17,18] Meyerowitz et al reported decreased decay in cancer patients with use of 0.05% sodium fluoride mouthwash[19]. Chamber et al compared intra oral fluoride release and stannous fluoride and reported similar reduction in caries.[20.21] Spak et al concluded daily sodium fluoride gel application comparable to 1.23 % fluoride gel application .[22]

The overall level of home oral care and awareness in low to negligible in our population. A stringent oral care program is essential with professional intervention, which is both economic and easy for patient to follow.

In our experience there are higher incidence of decay during first year after completion of cancer treatment specially radiotherapy for our patients. This is due to lack of awareness and difficulty to adhere to adequate oral hygiene during and after completion the cancer treatment.

Keeping this in consideration we propose use of more stringent professional fluoride application regime of once a month for first one year after oral cancer treatment completion and then at 3 monthly lifelong applications. This will be done along home use of fluoride mouthrinse and fluoride toothpaste lifelong. We would be comparing neutral sodium fluoride gel and varnish use at monthly and three monthly frequency

for first year after radiotherapy. We will be analyzing the clinical benefit of using the proposed fluoride type and frequency for our patients. To best of our knowledge there is no such study conducted before.

There is evidence for both fluoride gel and fluoride varnish as professional application in management of radiation decay in oral cancer patients. Fluoride varnish requires more strict post application routine as compared to gel application. While fluoride gel application has practical issues like gag reflex.[23]To best of our knowledge there are no randomized trial on which type of fluoride application is better for oral cancer patients. We aim to also analyze these two forms of professional fluoride applications in our population.

Economics also plays a major role in compliance to oral care for our population. We would also be assessing the economical burden oral care puts on overall expenses in cancer treatment.

The present study will attempt standardization of our oral care module and will test its effectiveness through analysis of outcome in terms of dental health indicators and quality of life among oral cancer patients. This will be done by using the observation design and following patients for a period of one year.

The study will be a prospective randomized controlled trial with two parallel groups. Intervention group will receive the monthly professional fluoride application as part of standard oral care protocol module while the control group will get four monthly professional fluoride application as part of oral care protocol module. Impact on

DMFT index will be the evaluation parameter. This will shed light on need and requirement of fluoride in cancer patients.

We would also be like to assess the burden and natural history of those oral cancer patients reporting to us who might have taken treatments from outside and had not received any standard oral care due to reasons mentioned in the protocol. We will be comparing their findings separately with our two experimental groups. This will help to highlight the importance of having a standard oral care protocol for all patients of oral cancer. Further it will provide us with information about the status of oral health in patients who have not received any preventive and supportive oral care as a part of their cancer treatment.

The objectives of this study are.

1. To compare the impact of two professional fluoride application regime on DMFT index among patients with oral & oro-pharyngeal cancer.

2. To validate, pilot test, document and standardize institutional oral care protocol for all patients of oral & oro-pharyngeal cancer.

2. Hypothesis

H0: There will be no difference in outcome between two professional fluoride application regimes regarding defined parameters in patients of oral & oro-pharyngeal cancer.

H1:Fluoride application regime with monthly professional application will have better outcome as compared to four monthly application in cancer patients regarding defined parameters.

3. Methods:

Objective 1: To compare the impact of two fluoride application regime on DMFT index among oral cancer patients.

Study design: Randomized controlled trial & observation design

After completion of pilot study, validation of institutional oral care protocol this study will start. The study will be a prospective Randomized controlled trial with parallel groups. Intervention group will be receiving monthly professional fluoride application and control group will be receiving four monthly professional fluoride application. Each group will further be divided in to two subgroups with either gel application or varnish application. The groups will be compared for DMFT index to compare the effectiveness of the fluoride application regime at 4 time points (0,1,6,12 months). The study will be conducted at Cancer research institute, Swami Rama Himalayan University, Dehradun (CRI, SRHU). All new cases of oral cancer receiving treatment will be enrolled.

Inclusion criteria:

1. Patient with histopathological diagnosis of squamous cell carcinoma of oral cavity & oro-pharynx.

2. Patient aged 18 years and above

3. More than 10 teeth in oral cavity

3. Gives consent

Exclusion criteria:

1. Patients with distant metastasis.

2. Previously received any kind cancer treatment.

3. Use of tobacco.

New patients with definitive histopathological diagnosis of oral cancer will be recruited from oncology OPD after taking informed and written consent according to Helsinki declaration. All eligible patients will be informed and explained by the consultant seeing them about the intent of the study and after giving the consent of participation they will be allocated into the group according to the random table chart provided by the biostatistician. **(Centralized randomization** Room no 004 Oncology OPD at CRI **)**

A designated person in-charge of random allocation will receive the table of random numbers chart and will make envelops with slips of either Group A (with gel or varnish application) designates as A-G & A-V and Group B (with gel or varnish application) designates as B-G & B-V inside it. We will be using '**S**equentially **N**umbered **O**paque **S**ealed **E**nvelopes' (SNOSE) which will be made in sets of 100 as per the random number chart with each numbered 1 to 100 and so on.

These envelops will be stored under lock and key under the designated in charge and will be handed over to researcher, who will open the envelop in a the designated sequence only when the participant reports to him. The research at no point will be aware about the random chart allocation and will only be revealed about the patient group at time of first interaction through a sealed envelop (concealment of allocation). The envelope will be opened in front of patient, which would reveal whether the patient is in Group A or Group B. Group A will receive standard oral care protocol with monthly fluoride regime, Group B will receive standard oral care protocol with quarterly fluoride regime. Further each group will be divided in two subgroup one will receive gel and other will receive varnish application. The **CONSORT** scheme will be adopted for conducting the trial. The researcher will not be involved in the randomization process and will only be aware once the allocation of patients to the group is completed.

The PICO criteria is defined as under

1. **P**articipants: All new oral cancer cases.

2. **I**ntervention: Monthly professional fluoride application with either gel or varnish.

3. **C**omparator: Four monthly professional fluoride application with either gel or varnish.

4. **O**utcome variable: Oral health & quality of life indicators; DMFT index.

Evaluation: Patients will be evaluated for set parameters at baseline, one month after completion of primary treatment, six month and one year after completion of cancer treatment. There will be no blinding of any kind. The patients will be kept on recall

for longer period to study effect on the oral health parameters but this will not be part of the present study.

Sample size: Present study will be a prospective randomized parallel group study with allocation ratio of 1:1. As there is no previously available data on frequency of fluoride application as proposed by us. We assume that fluoride monthly application will result in 60 % reduction in decay and quarterly application will result in 30 % reduction in decay at end of 1 year observation period. New patients with established diagnosis of oral cancer will be enrolled as per protocol. Sample of 60 patients in each group (intervention and control) is planned at 1% alpha and 90% power 95% confidence interval.

Sample size calculation:

$n = \{Z_{1-a/2} \sqrt{P_1(1-P_1)} + Z_{1-b} \sqrt{P_2(1-P_2)}\}^2 / (P_1-P_2)^2$

$n = 54$

We assume that monthly professional monthly fluoride application with standard oral care protocol will improve oral health and quality of life parameters by 60 % and Four monthly professional fluoride standard oral care protocol will improve oral health and quality of life parameters 30 % at one year after completion of the study. We will be considering taking 20% as attrition rate (20% of 54 = 10.8, rounded to 11);

The final sample size will be 66patients per group. (Subdivided in 33 patients in gel and varnish group)

The annual load of oral cancer reported at CRI SRHU is approximately 200. We will be randomly recruiting 66 cases in both groups. Each group will be further divided into two subgroups to receive either gel or varnish application.

Statistical analysis: The data will be collected and entered in MS excel 2010. Different statistical analysis will be performed using SPSS software version 22. Intention to treat analysis will be used for the analysis of data.

Trial evaluation and follow up:

The data will be evaluated on 6 monthly duration for adherence to set protocol with information to institutional ethical committee board.

Trial stopping rules:

The clinical trial will be stopped for any of the following reasons.

1. As per the recommendation of ethical committee board any patient with any ethical dilemma which would compromised his treatment will be taken out of the trial.

Trial stopping will not affect in any way the level of care the patient will need.

Ethical consideration: The study will be presented to institutional ethical committee of Swami Rama Himalayan University, for review and upon clearance from the committee, study will be started. All patients will be signing written informed consent with a right to stop and withdraw consent at any point of time during the trial. Any adverse event reported will be duly documented and reported

The study will be registered after the successful clearance of institutional ethical committee with The Clinical Trials Registry- India (CTRI), before starting enrolling

the first patient. In the present study we will be giving the standard of care of fluoride application i.e. 4 monthly to our control group and there is ambiguity whether monthly fluoride professional application given to intervention group will benefit the oral health. In these situation there are no ethical issues. In any rare case of any problem to the patient regarding the study, the trial monitoring committee will address it and decision of ethical committee in this regard will be considered final.

Any reason of withdrawal of patients consent / participation will in no manner effect the level of care and treatment protocol for these patients will remain same

3. Methods:

Objective 2: To validate, pilot test, document and standardize institutional oral care protocol for all patients of oral & oro-pharyngeal cancer.

Type of study: Validation & Pilot.

Duration: Two Months.

After obtaining the ethical clearance and acceptance of protocol by university validating process will start. For validating our oral care protocol, we will be inviting 6 experts from the filed of oncology care including dental experts, radiation oncologist, medical oncologist, surgical oncologist, nursing expert. First draft will be prepared through review of international guidelines. It will then be shared with the

experts for their comments. After necessary revisions a small group discussion moderated by the researcher will be done. After the consensus among the experts necessary changes will be done and the document will be considered valid. Validity will be judged on the set parameters.

Once the validity is established, pilot testing will be initiated and will include patients of oral cancer reporting to oncology OPD at CRI.

Sample size: The pilot study will be done for 10 consecutive patients (15% of sample size of randomized trial) and will be complete in one-month time frame.

Evaluation: Compliance of the patients with the oral care regime and their feedbacks will be documented. The pilot will also be used as an opportunity to probe into any potential hindrance in conduct of the study. Any problem identified will be addressed and resolved before starting the randomized trial.

Consent: A written informed consent of all the patients will be taken, patients will be informed that they are a part of pilot study and their data is being used to pilot the randomized trial. They will not be part of the aforementioned randomized trial.

Ethical considerations: The patients enrolled in the pilot study will receive the oral care protocol intervention and all the potential benefits if any.

To standardize institutional oral care protocol, after completion of piloting and validation we will observe the two arms of randomized trial participants for a year at 0,1,6,12 month period for quality of life and oral health indicators. (Defined in operational definition). (Observation design)

To document the effect of insufficient oral supportive care and its effect on oral health and quality of life, we would enroll patients who could not receive oral care for any reasons and will document their oral health status. Patients will be enrolled by total enumeration technique and these patients will be provided all supportive oral care once they come in our contact. (Observation design)

We will also estimate load and pattern of oral cancer cases reporting to Cancer research institute, Swami Rama Himalayan University. After obtaining the ethical clearance, acceptance of protocol by university and necessary permission from central

records this study will start. It will be the collection of retrospective data of number and type of oral cancer patients reported to CRI, SRHU in last 8 years. This will be done to document load and pattern of oral cancer in our region. The number of patients will be as per our central record database (2011-2018). Necessary permission will be taken for assessing the records. (Historical design retrospective)

4. Major expected findings and significance of the findings

The present study is conducted to standardized oral care module and assess the effect of two different professionally fluoride application regime on the outcome variable such as oral health indicators and quality of life in oral cancer patients.

Oral care is the most neglected aspect of care in oral cancer treatment in India due to various reasons ranging from economical burden onpatients to lack of integration of dental care in cancer treatment at majority of cancer treatment centers. There is a critical need of devising and providing oral care as basic standard of care for oral cancer patients.

Proposed outcome

1. Standardization and documentation of our institutional oral care protocol for cancer patients.

2. Effect of monthly versus four monthly professionally applied fluoride regime on defined outcomes of oral & oro-pharyngeal cancer patients

3. Efficiency and comparison of Varnish and gel type of fluoride professional application.

4. Identification of oral care and treatment needs in cancer patients.

5. Formulation of an economical oral care module for recourse limited countries and assessing oral care economical burden.

6. Integration of dental care services in oncology treatment as an essential supportive care for oral & oro-pharyngeal cancer patients.

7. Inclusion of dental oncology expert as a part of oncology cares team for oral & oro-pharyngeal cancer patients.

8. Documentation of prevalence and pattern of oral & oro-pharyngeal cancer in our region.