CHAPTER -3

MATERIALS & METHODS

3: MATERIALS AND METHODS

The present study was conducted in the Department of Dental Surgery, Cancer Research Institute, Swami Rama Himalayan University on patients who have received CT-RT for oral cancer. These patients were followed for a period of one year to evaluate changes in DMFT sores and OHIP-14 scores by the various fluoride intervention regimens. The duration of the present trial was two years and six months.

3.1 Study Design

3.1.1 Randomized Controlled Trial

The present study was started after the completion of the pilot and validation of institutional oral care protocol. It was a prospective randomized controlled trial (RCT) with parallel groups and an allocation ratio of 1:1. Groups received either monthly professional fluoride application or quarterly professional fluoride application with either varnish or gel preparation. No changes in the methodology were done after the commencement of the RCT.

3.1.2 Trial registry, Initiation, and Completion

The study was cleared by the institutional ethical committee at Swami Rama Himalayan University and registered with The Clinical Trials Registry- India (CTRI) vide registration number **CTRI/2019/08/020794.** The study commenced on 9th August 2019 with the enrollment of the first patient and concluded on 27th February 2022 after the completion of one-year recall of the last enrolled patient.

3.2 Eligibility criteria

New patients with definitive histopathological diagnosis of oral cancer will be recruited from oncology OPD at Cancer Research Institute, SRHU. Under-mentioned eligibility criteria for inclusion and exclusion were used.

3.2.1 Inclusion criteria

1. Patients aged 18 years and above who have given consent.
2. Patient with histopathological diagnosis of carcinoma of the oral cavity or receiving radiotherapy in the same region.

3.2.2 Exclusion criteria

1. Patients with distant metastasis at the time of enrollment in the study.
2. Previously received any kind of cancer treatment.

After taking informed and written consent as per the Helsinki declaration, all eligible patients were explained by the primary researcher the details of the study.

3.3 Intervention

All eligible participants were divided into two groups; Group A (monthly application) and Group B (Quarterly application) according to the frequency of fluoride application. (Chart 1)

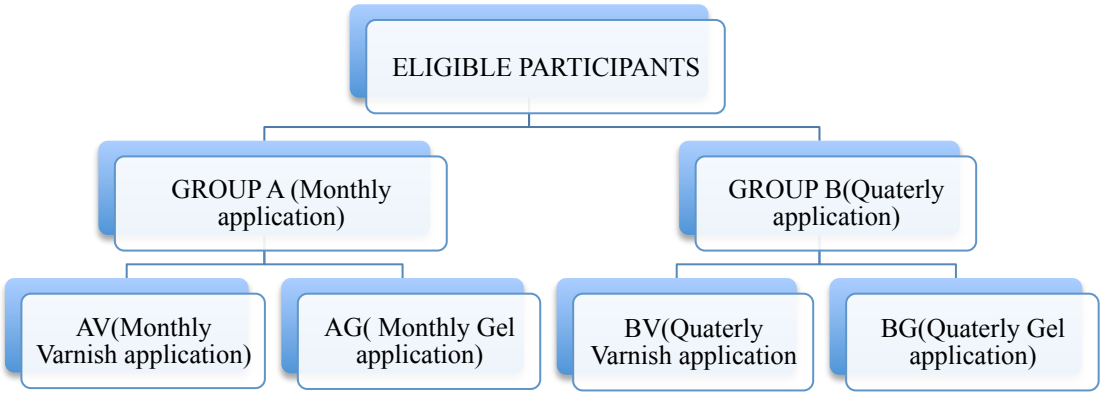

Chart 1: Intervention division flow chart

These two groups were further subdivided according to the type of fluoride used into V (varnish) and G (Gel). This resulted in 4 groups with 28 participants in **AV** (Monthly fluoride Varnish), 27 participants in **BV** (Quarterly fluoride Varnish), 27 participants in **AG** (Monthly fluoride Gel), and 29 participants in **BG** (Quarterly fluoride Gel). The consolidated statement of reporting trials (**CONSORT)** scheme was be adopted for conducting the trial.[87]

The primary researcher was not involved in the randomization process and become aware once the allocation of patients to the group was completed.

3.3.1 The PICO criteria

1. **P**articipants: All new oral carcinoma cases or head and neck carcinoma cases which included oral cavity in the field of radiation.

2. **I**ntervention: Monthly professional fluoride application with either gel or varnish.(AV &AG)

3. **C**omparator: Quarterly professional fluoride application with either gel or varnish.(BV & BG)
4. **O**utcome variable: DMFT index and (OHIP-14) Oral health & quality of life indicators.

3.3.2 Application of intervention

Topical Fluoride preparations were applied after removing any food debris or plaque from the tooth surfaces. Tooth surfaces were isolated with help of high evacuation intraoral suction and dried with compressed air before application.

a) Varnish application: On clean dry tooth surfaces Flouritop SR varnish (ICPA laboratories) with 23000 ppm was used. It was applied with help of an applicator brush tip in painting motions over the hard surfaces of the clean dry tooth for a period of four minutes.

b) Gel application: on clean dry tooth surfaces Flucogel (Septodont Pvt. Ltd.) with 12500 ppm was used. It was applied with help of disposable styrofoam trays. A thin ribbon of gel was poured on the upper and lower tray and the patients were instructed to bite on it for a period of four minutes.

During all applications, patients were instructed not to swallow any saliva and a high evacuation intraoral suction was used for this. On completion of the application procedures, participants were instructed to not swallow saliva or drink fluids for one hour. After an hour, rinsing twice with plain water was advised before consuming fluids. No food was allowed for a period of six hours and patients were reinforced with oral care and brushing techniques.

3.4 Study Outcome

Baseline data was collected for demographic, age, gender, education, income, and cancer site. Personal history for use of smokeless tobacco, alcohol, and smoking, brushing aid type, and brushing frequency was also reported. Dental treatment such as extraction, restoration, and Root canal treatment was documented along with the financial burden on patients. Cancer treatment-related information such as cancer histopathology, chemotherapy, radiotherapy dose, surgery, mucositis, and trismus was also recorded.

3.4.1 Primary outcome

The primary outcome was Decayed Missed & Filled Teeth (DMFT) scores, which was a clinical examination along with radiographic confirmation done by primary research (Dental surgeon) for all four-intervention groups. DMFT was calculated as per DMFT Index (Henry Klein modified by World Health Organization in 1986) by the researcher as per standard criteria of oral examination and reporting.[88, 89] DT scores were Decayed teeth due to caries, MT scores were Missed teeth due to caries, and FT scores were Filled teeth due to caries**.** DMFT Scores were the summation of all the above three scores i.e. DT, MT, and FT. All permanent teeth were examined, Calculation of DMFT scores along with DT, MT, and FT scores per person was done at baseline, one month, six months, and one year.

Hindi translated and validated version of the Oral health impact profile questionnaire (OHIP-14) was used to record the oral health-related quality of life scores.[90] These scores were taken at baseline, one month, six months, and one year

after completion of treatment. OHIP-14 questionnaire comprised of 14 questions, each question has a response from 0 to 4 on a five-point Likert scale '0' as never and '4' as very often. The questionnaire was a subjective response type and was administered by the researcher. Responses were recorded in the patient record forms for all visits.

The questionnaire was divided into seven domains comprising two questions each. The seven domains were, a) functional limitation, b) physical disability, c) physical pain, d) psychological discomfort, e) psychological disability, f) social disability, and g) handicap. The OHIP-14 score range from 0 to 56 values, and each of the seven-domain range from 0 to 8. The scores were calculated for all participants at baseline, one month, six months, and one year.

3.4.2 Secondary study outcome

The secondary outcome was regarding the validation study of supportive oral care protocol (SOCP). This was published in the Indian Journal of surgical oncology in 2020. Fifteen dental experts and six oncology experts reviewed the 41 points SOCP that was divided into three levels of care. Inter-rater validity agreement (IVC) was calculated and assessed for validation.

3.5 Sample size

3.5.1 Calculation:

To the best of our knowledge, there was no previously available published data on the frequency of fluoride application and type of fluoride in a population similar to ours. We assume that monthly fluoride application would result in a 60 %

reduction in decay and quarterly application would result in a 30 % reduction in decay at end of one-year observation period. To calculate sample size at 1% alpha and 90% power 95% confidence interval under mentioned statistical formulae was employed.

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

n=54

An attrition rate of 20% was taken (20% of 54 = 10.8, rounded to 11) making the final sample size of 66 patients per group in monthly and quarterly application arms. These were further subdivided into 33 patients each in the gel and varnish group. Thus the final sample size for each of the four intervention groups was 27 participants. An additional 20% attrition rate; the final sample size was 33 participants per group.

3.5.2At the completion of the Trial:

The present trial was designed following the CONSORT 2010 checklist. A total of 175 participants were assessed for eligibility to be enrolled in the present trial. 149 patients were eligible at the enrollment stage and were randomized to receive an allocation. AV, AG, BV & BG received 38, 37, 38, and 37 participants respectively.

After the first visit loss to follow-up for AV, AG, BV & BG were 10, 10, 11 and 8 respectively. A total of 111 participants completed the study in all aspects; the reason for exclusion from the trial were lost to follow up, expired, change treatment midway, or did not report to follow up for any reasons. The final numbers of

participants who completed the study and were used for analysis for AV, AG, and BV& BG were 28, 27, 27 & 29. The details of loss to follow up or discontinued treatment were death, distant metastasis, shifting to Ayurveda treatment, and COVID-19 pandemic issues. (Chart 2)

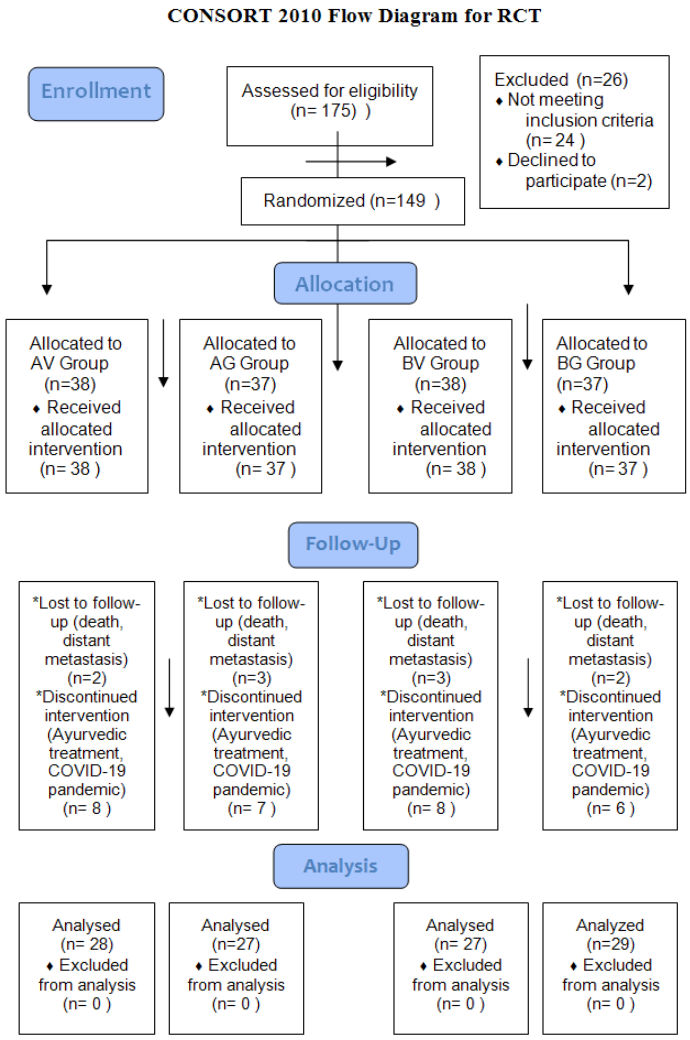

Chart 2: CONSORT Flow diagram for a randomized controlled trial, patient enrollment, follow-up, and analysis details.

The duration of the study was extended to complete the required sample size this was done because multiple patients were lost to follow-up and did not continue their treatment due to COVID 19 pandemic.

3.6 Trial check parameters

3.6.1 Trial evaluation, follow-up, and stopping rules

The data evaluation was done on 6 monthly duration for adherence to set protocol with information to the institutional ethical committee board. The clinical trial would be stopped on the recommendation of the ethical committee board. Any patient with any ethical dilemma, which would compromise his treatment, would be removed from the trial. Trial stopping would not affect in any way the level of care the patient needs. Any reason for withdrawal of a patient's consent will not affect the level of care and treatment protocol for these patients would remain the same.

3.6.2 Ethical consideration

The study was approved vide letter number SRHU/HIMS/ETHICS/2019/115 by the institutional Ethics Committee of Swami Rama Himalayan University, for review and upon clearance from the committee, the study was started. All patients signed written informed consent with a right to stop and withdraw consent at any point of time during the trial. Any adverse event reported would be duly documented and reported.

In the present trial, patients were given the standard of care as quarterly fluoride application and there was ambiguity about whether monthly fluoride professional application would benefit oral health. In these situations, there are no ethical issues to consider as all groups received a basic level of standard of care. In any rare case of any problem with the patient regarding the study, the trial monitoring committee had full authority and its decision was final and binding.

3.7 Randomization details

Participation was allocated intervention according to the random table chart provided by the biostatistician. Randomization was non-restricted and used random numbers by random number generation software.

3.7.1 Allocation, concealment mechanism, and Implementation

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

These envelopes were stored under lock and key under the designated in-charge (Mr. BDB) and were handed over to the primary researcher, who opened the envelope in a designated sequence only when the participant reports to him. The primary researcher at no point was aware of the random chart allocation. The researcher only became aware at the time of first interaction with the patient (concealment of allocation). The envelope was opened in front of the patient, which revealed which intervention the patient was allotted.

3.7.2 Evaluation and blinding:

Patients were evaluated for set parameters at baseline, (before starting CTRT), followed at one month, six months, and one year after completion of CTRT. There was no blinding of any kind in the present trial.

3.7 Statistical analysis:

The data were collected and entered in MS excel 2010. As the data followed a non-normal distribution, non-parametric tests were employed to conduct statistical analysis in SPSS software version 22. Intention to treat analysis was used for analyzing the dataset.

Frequency and percentage were used to describe the data at baseline. As the data was non-normal; the median and interquartile range was used to describe primary outcomes i.e. DMFT scores and OHIP scores. Mean and standard deviation were also reported to understand the data Pattern.

For intra-group comparison at baseline, one month, six months, and one year; Freidman Non-parametric test was used. On significant result post hoc test of Related samples, Freidman's two-way analysis of variance by ranks was used.

For intergroup comparison amongst AV, AG, BV, and BG groups Kruskal-Wallis Non-parametric test was employed. On getting significant results, a post hoc test Kruskal-Wallis was used.

Spearman’s correlation was used to analyze the relationship between DMFT and OHIP indices. An Independent sample student t-test was used to analyze OHIP and DMFT scores with mouth opening.

For validation of SOCP, inter-rater agreement (IVC) was calculated and a value of IVC of more than 0.78 was considered significant for agreement between experts.