No: UHS/ Education/126-22/2314
13-04-2022

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SUBJECT: APPROVAL OF SYNOPSIS

Revised synopsis entitled "***Comparison between two mouth washes in the prevention and management of oral mucositis during radiotherapy of head and neck cancer patients***" submitted by you for M.Phil (Oral Biology) has been approved by the Vice Chancellor on behalf of the Advanced Studies & Research Board.

Prof. Fozia Farzana, Ex-Head, Department of Anatomy, Postgraduate Medical Institute, Lahore, has been appointed as your supervisor, and Dr. Muhammad Sharjeel Ilyas, Associate Professor of Oral Biology, at the institute, as co- supervisor.

Dr. Hummad Hussain
Deputy Registrar (Academics)
For Registrar

CC:

- Prof. Fozia Farzana, Ex-Head, Department of Anatomy, Postgraduate Medical Institute, Lahore
- Dr. Muhammad Sharjeel Ilyas, Associate professor of Oral Biology, Postgraduate Medical Institute, Lahore
- Principal, Postgraduate Medical Institute, Lahore
- Controller of Examinations
- P.S.O to Vice Chancellor
- P.S to Registrar

INTRODUCTION

Oral cavity is lined by stratified Squamous epithelium with a very high mitotic activity in the basal layer of this epithelium. Oral cavity is divided into various subsites with keratinized or non keratinized epithelial lining. In Pakistan the prevalence of oral cancer is 10 %(Markopoulos, 2012). The increasing incidence of oral cancers in Indian subcontinent is due to lack of oral hygiene, tobacco use, chewing tobacco leaves and smoking (Khan, 2012). Treatment modalities for oral cancers are mainly by surgery with adjuvant radiotherapy, chemotherapy or both (Syrigos et al., 2009). Use of radiations for the treatment of cancer causes breakage of double stranded DNA that leads to cell death. Radiation affects cell cycle necessary for cell growth and apoptosis (Baskar et al., 2012). Most patients with head and neck carcinomas are given a dose between 50-70 Grays for treatment, usually given in 2 Grays per fraction once a day for 5 days a week over 5-7 weeks depending upon the volume and location of the tumor (Bernier and Bentezen, 2006). As the radiation affects rapidly dividing cells of cancer, it also damages oral mucosa causing oral mucositis, the most common complication of radiotherapy. Other complications are xerostomia, hair loss, nausea, diarrhea, leucopenia, cervical caries, dysphagia, fatigue and weight loss (Franklin and Berkey, 2010).

Oral mucositis of varying degrees occurs in almost 100% patients receiving radiotherapy for head and neck cancers and up to 80% of patients receiving chemotherapy and HSCT (Rubenstein et al., 2004).

Expression of 48 salivary proteins including MIF was found related to an increased risk for the development of OM during radiotherapy of head and neck cancer patients (Jehmlich et al., 2015). Different immune and non immune cells e.g eosinophils, neutrophils, monocytes/macrophages, endothelial cells and epithelial cells express MIF (Camila Cristina Guimarães Nobre et al., 2017). It is released in response to different stimuli like hypoxia, microbial products and proliferative signals. It promotes the recruitment and migration of leukocytes towards the site of inflammation and infection. MIF increases cytokine expression i.e TNF-α, IL-6 and prostaglandins (Yveth Marlene Ortiz-Garcia et al., 2019).

There are many different agents used for the prevention and management of oral mucositis. Such as topical cytoprotective agents e.g sucralfate, topical or systemic antioxidants e.g. amifostine, vitamin-E, bio-stimulant (granulocyte macrophage colony stimulating factor), low laser therapy and antibacterial agents like lozenges (Caballero et al., 2011). Use of

honey, glycerine thymole, glycerine iodide, chlorhexidine, benzydamine, normal saline and supersaturated calcium phosphate rinse and some other topical solutions has also been reported to be effective in the prevention and management of oral mucositis but effectiveness of each of these solutions varies greatly (Karthaus et al., 1999). Many studies have been conducted previously to compare the effectiveness of various mouthwashes in prevention and management of oral mucositis. This study is planned to compare the effectiveness of Benzydaminehydrochloride with super saturated calcium phosphate solution in prevention and management of oral mucositis patients undergoing radiotherapy for oral cancers.

LITERATURE REVIEW

Oral cavity is lined by a mucous membrane that consists of stratified Squamous epithelium and lamina propria. The deeper layer stratum basale of stratified squamous epithelium has high rate of mitotic activity. The underlying connective tissue (lamina propria) plays a significant role in epithelial differentiation. The differentiation of epithelium in oral cavity is regulated by growth factors. Normal oral mucosa is paler pink but inflamed mucosa appears red (Nanci, 2012).

Cancer is defined as uncontrolled and abnormal growth of cells. Eighth most common type of cancer is head and neck cancer (Pai and Westra,2009). Of all the cancers, 2%-4% of the cancers are oral cancers (Markopoulos, 2012). In Pakistan, the prevalence of oral cancers is 10 % (Markopoulos, 2012). Lack of oral hygiene, tobacco chewing and smoking are the causes of increased oral cancer incidence in the Subcontinent (Khan, 2012). Treatment modalities for oral cancers include surgery with adjuvant radiotherapy, chemotherapy or both (Syrigos et al., 2009). Use of radiations leads to breakage of double stranded DNA causing cell death. Radiation affects cell cycle necessary for cell growth and apoptosis (Baskar et al., 2012). Oral mucositis is a well-established complication of antineoplastic therapy for head and neck cancer patients, defined as inflammatory lesion of oral mucosa characterized by erythema, edema, mucosal shedding and ulceration (Sheibani et al.,2014). Judith et al.(2012) also described oral mucositis as an inflammatory lesion typically manifesting as atrophy, swelling, erythema, ulceration and pseudomembrane formation. Sonis (2004a, 2004c) was of the opinion that oral mucositis is not just damage to surface epithelium but it involves a multitude of molecular events targeting underlying submucosa. Later studies by Khannal et al.(2010) also supported his opinion. Oral mucositis is described in five overlapping phases: initiation, up regulation and message generation, signaling and amplification, ulceration, healing (Sonis, 2004b).

Any structure, substance secreted by the tumor, metabolic pathway, or process that can be employed for diagnosis, prognosis and prediction of pathogenic processes or pharmacological responses to a therapeutic intervention, which is measureable, reproducible and accurate is called a biomarker (Ana Gabriela Costa Normando et al., 2017). Sha –sha Wang et al. (2017) was of the opinion that MIF regulates angiogenesis, epithelial-mesenchymal transition (EMT), hypoxia and cell cycle in different types of cancers including head and neck cancers so MIF is a promising biomarker. Kindt et al., proved that MIF/CD74 pathway was involved

in the HNSCC progression.At first it was thought that MIF inhibits macrophage migration (Bucala R, et al., 2007). But later on extensive studies on MIF showed that it acts mainly as pro inflammatory cytokine (Bernhagen J et al., 1993). MIF is correlated with increased risk of developing severe OM post- radiotherapy (Nata`lia Rangel Palmier et al., 2020).

Oral mucositis is a well-established complication of antineoplastic therapy for head and neck cancers but its prophylaxis and treatment is not clearly defined and consists mainly of supportive care. Use of different agents like honey, glycerine thymole, glycerine iodide, chlorhexidine, benzydamine, normal saline and supersaturated calcium phosphate rinse and some other topical solutions has also been reported with variable effectiveness of each, in the prevention and management of oral (Karthaus et al., 1999).

Supersaturated calcium phosphate rinse (SCPR) was found to be effective in lowering incidence and severity of oral mucositis in patients receiving radiotherapy (Thomson, 2011) and reducing the oral pain (Quinn, 2013). Miyamoto et al. (2009) andNicolatou-Galitis et al. (2010) supported the role of supersaturated calcium phosphate rinse in the prevention and treatment of oral mucositis in patients receiving antineoplastic therapy. Markiewicz et al. (2012) also proved positive effects of SCPRon oral mucositis in patients undergoing hematopoietic stem cell transplantation. The distinguishing feature of calcium phosphate as compared to all other oral rinses is that it has high concentration of calcium and phosphate ions which exert their beneficial effect by diffusing into intercellular spaces of mucosal epithelium and permeating mucosal lesions. Calcium ions play important role in inflammatory process, blood clotting cascade and tissue repair and fibrin production. Whereas phosphate ions play a vital role in regulating the voltage potential inside the cell, facilitating intracellular signaling which are very much important for the repair and protection of damaged mucosal surface (Papas et al., 2003). Calcium phosphate also reduces the acidity in oral cavity. This may play an important role in avoiding mucosal damage, thus creating more favorable environment for diminishing mucositis symptoms (Markiewicz et al., 2012).

Benzydamine (BNZ) is non steroidal agent having anti-inflammatory, analgesic/ anesthetic and antimicrobial effects (Karthaus et al., 1999). Benzydamine oral rinse can be considered as an effective, safe and well tolerated solution (Sheibani et al., 2014). But with the use of benzydamine oral rinse, following side effects are observed in the patients: cough, dry mouth with thirst, stinging and burning sensation,taste alteration, throat irritation and headache has also been reported (Karthaus et al., 1999).Because of initial oral discomfort and burning

sensation patients discontinue participation in the trial(Putwatana et al., 2009).The anti-inflammatory activity of BNZ may be due to its membrane-stabilizing effect or to inhibition of the synthesis of inflammatory cytokines and TNF-α. The antibacterial property of benzydamine may assist its anti-inflammatory activity when applied to the mouth. (Quane et al., 1998).

Rationale of this study is to compare the effectiveness of Benzydamine hydrochloride with super saturated calcium phosphate solution and correlation of MIF levels in prevention and management of oral mucositis in patients undergoing radiotherapy for oral cancers.

Hypothesis:

Oral rinses of super saturated calcium phosphate solution in comparison with benzydamine hydrochloride oral rinse, will be more effective in reducing MIF levels and the severity of oral mucositis induced by radiotherapy in head and neck cancer patients.

Objective:

To compare and correlate MIF levels with onset and severity of radiation induced mucositis in head and neck cancer patients by using super saturated calcium phosphate solution and benzydamine hydrochloride.

Materials and methods

Study design: Randomized Controlled Trial.

Study setting: The research will be carried out in Oncology Department Mayo hospital, Lahore.

Study duration: 9-12 months after approval of synopsis.

Sample size: The sample size of 42 head and neck cancer patients will be divided into two equal groups of 21 each keeping the power of study equal to 90% and level of significance equal to 5%.

$$n = \frac{\left(Z_{1-\alpha}\sqrt{2\bar{p}(1-\bar{p})} + Z_{1-\beta}\sqrt{p_1(1-p_1)p_2(1-p_2)}\right)^2}{(p_1 - p_2)^2}$$

(Sample Size determination in health studies version 2.0.21 WHO)

$Z_{1-\beta}$ is the desired power of study = 90%

$Z_{1-\alpha/2}$ is the desired level of significance = 5%

P_1 is the anticipated proportion of grade 2 and 3in SCPR group = 10%

P_2 is the anticipated proportion of grade 2 and 3 in BZD group = 50%

n is the calculated sample size in each group = 21

(Markiewicz et al., 2012)

Sampling technique and Randomization: 42 head and neck cancer patients will be selected using non probability convenient sampling. They will be randomly allocated into two groups using balloting method.

Inclusion criteria:

- Patients of either gender (age group 30-70 years) with any histological type of head and neck cancers having a treatment plan to receive radiotherapy.

Exclusion criteria:

- Patients with poorly controlled diabetes mellitus
- Patients with prior xerostomia
- Patients with a history of chemo/radiotherapy

PROCEDURE

42 patients of either gender and age group 30-70 years with head and neck cancer will be selected. Informed consent will be obtained from all the patients (Annex-I, Annex-II). Selected patients will have no history of previous radiotherapy or any other major systemic disease. There will be no evidence of oral mucositis before the commencement of study. The patients will be assigned into two groups by non-probability convenient sampling and their study groups will be as follows:

Table -1

Groups	**Number of patients**	**Oral Rinse to be Used**
A	21	Benzydamine Hydrochloride (Experimental group 1)
B	21	Super saturated calcium phosphate solution (Experimental group 2)

Patients will be examined before starting radiotherapy. Radiation therapy will be started at a dose of 2 Gray per fraction for 5 days a week up to a total dose of 50-70 Grays in total 6 weeks.

In the experimental group1patients will be asked to rinse with 15 ml benzydamine hydrochloride solution for three times daily from the day radiation therapy will start till the radiation therapy continues (6 weeks).

In the experimental group 2 patients will be asked to rinse with 30 ml supersaturated calcium phosphate solution for four times daily from the day radiation therapy will start till the radiation therapy continues (6 weeks).supersaturated calcium phosphate solution will be prepared and dispensed(Annex III). It will be stored at room temperature.

Examination of oral mucosa will be performed on all patients at the beginning of treatment and will be continued weekly up to the end of radiotherapy (6 weeks) by visual assessment. Grade 0-4 of oral mucositis by WHO will be assessed using battery operated light.

Whole saliva sample will be collected from each participant of both the groups before the commencement of radiotherapy. Participants will rinse their mouth and then 3mL of whole saliva will be collected in disposable test tubes. Samples will be refrigerated at -80°c until

ELISA is performed to quantify MIF levels. Saliva sample will also be collected after 3 weeks of end of radiotherapy and will be stored following the same protocol.

MIF quantification will be done by sandwich ELISA method (BioLegend® Legend Max TM Human Active MIF, Cat. No. 438408) according to manufacturer's instructions.

Grade 0: No change in oral mucosa.

Grade 1 (Mild): Only mucosal erythema, no ulcers, oral/gingival mucosa is red and shiny. Gingiva may appear swollen.

Grade 2 (Moderate): Erythema plus focal ulceratiaons, able to eat and drink.

Grade 3 (Severe): Confluent ulcers, can take liquid diet only.

Grade 4 (Un acceptable): Massive ulcers, unable to eat and drink.

Study Variables

Qualitative variable:

- **Onset and Severity/progression of Oral Mucositis**

  WHO scale for grading oral mucositis (Cheng and Yeun., 2006)

  Grade 0: No change in oral mucosa.

  Grade 1 (Mild): Only mucosal erythema, no ulcers, oral/gingival mucosa is red and shiny. Gingiva may appear swollen.

  Grade 2 (Moderate): Erythema plus focal ulceratiaons, able to eat and drink.

  Grade 3 (Severe): Confluent ulcers, can take liquid diet only.

  Grade 4 (Un acceptable): Massive ulcers, unable to eat and drink.

Statistical Analysis

The data will be entered and analyzed using SPSS25 (full form). Normality of data will be calculated by Shapiro Wilk test. The quantitative data will be analyzed using Student-T test to determine the mean difference in quantitative variables between groups. Mean ± SD will be given for quantitative variable (ELISA macrophage migratory inhibitory factor levels). Chi square test will be used for analysis of qualitative variable (The onset and severity of oral mucositis). A *p*- value of ≤ to 0.05 will be considered significant.

Table-2

Follow up plan for onset and progression of oral mucositis during radiotherapy course

	Week 1	Week 2	Week 3	Week 4	Week 5	Week6	Total
Experimental group 1							
G 0							
G 1							
G 2							
G 3							
G 4							
Experimental group 2							
G 0							
G 1							
G 2							
G 3							
G 4							

Table -3

Comparison of oral mucositis at the end of radiotherapy

Grade of oral mucositis	Experimental group 1	Experimental group 2	P-value
G0			
G1			
G2			
G3			
G4			

Patient characteristics

Table-4

	Experimental group 1	Experimental Group 2	Mean S.D	P-value
Age of patient				
Duration of radiotherapy				

Table-5

	Male to female ratio (M:F)
Experimental group 1	
Experimental group 2	

Annex-I

CONSENT FORM

Date …… OPD #.....

I, hereby, undertake that for the treatment of cancer, radiotherapy procedure has been explained to me. I know that application of Oral Rinse during radiotherapy has no side effects for me and this is due to research purpose.

Signatures of Patient

Name of Patient

Age/Sex

Annex III

Super saturated calcium phosphate solution will be prepared according to the following formulation: Dibasic sodium phosphate 0.032, monobasic sodium phosphate 0.009, calcium chloride 0.052, sodium chloride 0.569, purified water; supersaturated calcium phosphate rinse; contains sodium 71mg/30mL dose. It will be dispensed in a glass container of 200 ml and storage will be at room temperature. Preparation and dispensing of caphosol solution will be done by Fazal Din's Pharmacy, Mall road, Lahore.

Outcome and utilization:

The distinguishing feature of calcium phosphate as compared to all other oral rinses is because of high concentration of calcium and phosphate ions which exert their beneficial effect by diffusing into intercellular spaces and of mucosal epithelium and permeating mucosal lesions, thus creating more favorable environment for diminishing oral mucositis symptoms which will therefore improve the quality of life of patients with head and neck cancers undergoing radiotherapy

Plan of Work

Year	1-2	3	4	5	6	7	8	9-10	11	12
Application for funding										
Procurement of research material										
Research Project										
Observation & Collection of data										
Thesis writing										

Estimated Cost of the Project

S. No	Name of Items	Quantity	Unit cost (Rs)	Total cost (Rs)
1.	Benzydamine hydrochloride	40L	85 Rs per 200 mL	17000/-
2.	Super saturated calcium phosphate	106 L	100 Rs per 200 mL	53000/-
3.	Light source	1	400/-	400/-
4.	ELISA kit			
	Total Cost	-	-	**Rs.70,400/-**

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