Electronic Physician (ISSN: 2008-5842) http://www.ephysician.ir
November 2015, Volume: 7, Issue: 7, Pages: 1535-1541, DOI: http://dx.doi.org/10.19082/1535

The effect of casein phosphopeptide amorphous calcium phosphate fluoride paste (CPP-ACPF) on oral and salivary conditions of patients undergoing chemotherapy: A randomized controlled clinical trial

Sepideh Banava[1], Mohammad Houshyari[2], Tahmineh Safaie[3]

[1] DDS, M.Sc. in Restorative Dentistry and Dental Materials, Assistant Professor, Islamic Azad University, Dental Branch, Tehran, Iran
[2] Assistant Professor, Shohada-e-Tajrish Hospital, Department of Radiation Oncology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Dentist, Tehran, Iran

Type of article: Original

Abstract

Background: Oral and saliva conditions of patients undergoing chemotherapy is often affected by the medication they receive. Up to now, no appropriate medication that possesses the positive effects of chemotherapy without presenting oral complications has been introduced.

Objective: The aim of this study was to assess the clinical effects of CPP-ACPF paste on the oral and salivary status of patients undergoing chemotherapy.

Methods: From October 2013 to April 2014, 20 patients in chemotherapy treatment plans and who met the inclusion criteria enrolled in this randomized parallel single-blind controlled clinical trial in Shohada-e-Tajrish Hospital in Tehran, Iran. Patients were divided into two groups: 1) patients received their daily medication of cancer therapy center (group 1, control); 2) patients applied CPP-ACPF Crème (MI paste plus, GC USA) twice a day as instructed (group 2). The baseline status of oral conditions of patients (mucositis, dry mouth, infection, diminished tasting sense, difficulty in food intake, burning sensation of mucosa, saliva and dental plaque pH, rest and stimulated saliva, buffering capacity of saliva) were recorded and reevaluated after 21 and 42 days. The data were analyzed with a Mann-Whitney U-test.

Results: A total of 20 patients were allocated randomly to groups 1 and 2. The Mann-Whitney U-test showed that application of CPP-ACPF paste twice daily did not cause any significant difference in oral complication of the subject group compared with the control group ($p>0.05$). Among salivary signs, resting and stimulated saliva rates and saliva buffering capacity had significantly altered in the CPP-ACPF group in day 21 and 42 in comparison with those of the control group ($p<0.05$).

Conclusion: Application of CPP-ACPF paste before and during chemotherapy can improve the salivary status of patients undergoing this treatment.

Trial registration: The trial is registered at the U.S. National Institutes of Health (https://www.clinicaltrials.gov) with the identification number NCT01737307.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Keywords: Oral complication, dental plaque, saliva, casein phosphopeptide amorphous calcium phosphate

1. Introduction

The oral and salivary status of patients undergoing chemotherapy is often affected by medications for saliva reduction and increase the risk of dental caries (1, 2). Chemotherapy has a direct relationship with oral cavity tissues such as teeth, salivary glands, and oral mucosa (3, 4). The oral cavity gets dry during chemotherapy, which causes an increase in the risk of dental caries (5). As of today, no effective protocol has been recognized to prevent damage

Corresponding author:
Dr. Mohammad Houshyari, Shohada-e-Tajrish Hospital, Department of Radiation Oncology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Tel: +989123890621, Fax: +982122739200, E-mail: dr.mhoushyari@gmail.com
Received: April 13, 2015, Accepted: July 14, 2015, Published: November 2015
iThenticate screening: October 25, 2015, English editing: November 03, 2015, Quality control: November 10, 2015

to the oral cavity caused by chemotherapy (3). During the last 25 years, medical and dental articles have discussed the importance of oral care in the prevention of side effects from chemotherapeutic drugs, but effective features against these drugs has yet to be introduced, although it has been emphasized that any suggested substance should not be toxic, should not cause tooth decalcification, has moisturizing ability, and has an acceptable taste. Every patient with cancer should receive a complete oral examination before starting his or her chemotherapy, which can limit the side effects (6). At the beginning of chemotherapy, proper oral hygiene method should be instructed to the patients. Preventive protocols include using saline-bicarbonate, chlorhexidine, fluoride, and calcium-phosphate-containing mouthwash. Saliva stimulators such as gels, mouthwash containing peptides, mouth spray, and liquid and bio-active saliva stimulator can be useful as well (3, 5, 6). According to Recaldent Technology, Reynold presented CPP-ACP (casein phosphopeptides-amorphous calcium phosphate) in 1997. This product is known by the trade name of GC Tooth Mousse or MI paste and is formed from two parts. The protein part contains casein phosphopeptide (CPP) and the mineral part contains amorphous calcium phosphate (ACP= Ca3 (PO4)2 – nH2O). The calcium and phosphate in this component are amorphous, sol, and surrounded by phosphorus terminals; thus, it prevents early sedimentation of calcium and phosphate crystals before reaching the tooth surfaces. When applied in the mouth, CPP-ACP binds to teeth, pellicle, plaque, and soft tissue surfaces localizing bioavailable calcium and phosphate. The incorporation of fluoride with CPP-ACP introduced GC Tooth Mousse Plus or MI Paste Plus, which contains 10% CPP-ACP and 0.2% (900 ppm) NaF [it is called CPP-ACPF] (7). There are several studies showing benefits of applying CPP-ACP and CPP-ACPF pastes in remineralization of tooth structure in various groups of patients (8-10). As there has been no significant study about the effects of this material on the oral and salivary status of patients undergoing chemotherapy, this study was done to assess the effect of CPP-ACPF paste on the oral and salivary status of patients undergoing chemotherapy in Shohada-e-Tajrish Hospital (Tehran, Iran) to use this product in the patients treatment protocols by oncologists to utilize its benefit.

2. Material and Methods

2.1. Trial design and participants

The design of this study was a randomized parallel single-blind controlled clinical trial. After coordination with the related organizations, 20 patients being treated for cancer in Shohada-e-Tajrish Hospital were selected. The patients with the following inclusion criteria enrolled in the study after signing the informed consent form: cancer diagnosis, which required chemotherapy, older than 12 years old age, no systemic diseases, no head and neck cancer, and having at least 10 teeth. In the first stage, a data entry form was completed for each patient, and then they entered randomly in either the control group or study group.

2.2. Interventions

Patients in the control group (10 patients) received the preventive protocol of their treatment center. Patients in the study group (10 patients), in addition to the preventive protocol of their treatment center, as instructed, applied CPP-ACPF paste with their fingers (MI Paste Plus, GC, USA) twice daily for at least 5 minutes (written instructions for application was given to each patient). Every week, the patients were controlled to see if they correctly used the paste. Thereafter, the data entry form was completed for each of the patients after 21 and 42 days. In the data form of each patient, age, sex, type of cancer, prescribed medication, smoking, alcohol consumption, and wearing a denture were recorded. Then, the oral status of each patient was recorded by evaluating the mucositis (by WHO index and according to the oncologist diagnosis as Grade 0=no change; Grade 1=soreness; Grade 2=erythema [redness]; ulcers, can eat solids; Grade 3=ulcers, requires a liquid diet; Grade 4=severe ulcers prohibiting oral intake) Xerostomia, burning sensation in mouth, dysgeusia, complications in swallowing (by asking the patient) and infection (inspection of the oral cavity) (11,12).

2.3. Outcomes

The salivary status of the participants were evaluated by saliva and pH kits (GC saliva check kit, GC plaque indicator kit, GC America, USA) as described below:

1) For testing the resting saliva, the lower lip was extended, and labial mucosa was gently blotted with a small piece of gauze. Mucosa was observed under good light. If the droplets of saliva were observed in 30-60 seconds, the resting flow was considered as normal; if they were seen in greater than 60 seconds, it was considered low.

2) For testing the stimulated saliva, the patient was instructed to chew a piece of wax. After 30 seconds, the patient expectorated into the spittoon for 5 minutes. If the quantity of saliva was less than 3.5 ml, it was considered very low. If it was between 3.5–5 ml, it was considered low; if it was more than 5 ml, it was considered as normal.

3) Buffering capacity was evaluated by dropping saliva collection with a pipette on a buffer test strip and comparing it with the conversation table of the kit after 2 minutes. Buffering capacity between 0-5 was considered very low, between 6-9 was recorded as low, and between 10-12 was considered as normal.
4) Saliva pH measurement was done by placing a pH strip in a gathered sample of resting saliva from the patient for 10 seconds. pH between 5.0 to 5.8 was considered highly acidic, pH between 6.0 to 6.6 considered moderately acidic, and pH between 6.8 and 7.8 considered healthy.
5) If the patient were unable to brush his or her teeth because of problems like thrombocytopenia or any other blood problem during treatment, it would be recorded. Patients were examined again in the same described method in the follow-up dates of 21 and 42 days after the baseline examination.

2.4. Sampling
According to statistical analysis by the statistician and related articles, this study was conducted on 20 patients with the diagnosis of the cancer who accepted to participate in the study.

2.5. Statistical methods
In the follow-up sessions, each patient was evaluated according to the various variables as previously mentioned. The data were analyzed by Mann-Whitney and Friedmann statistical tests with alpha set at 0.05.

2.6. Research ethics
The ethics committee in the radiation oncology department at Shahid Beheshti University has approved this trial research. The patients signed informed consent forms before participating in the study. The study evaluator remained in contact with the patients during the study and follow-up times in case they experience problems, especially in the case group, which should have applied the CPP-ACPF paste.

3. Results
3.1. Participant flow
The results of this study, which evaluated the effect of CPP-ACPF on oral situations of patients undergoing chemotherapy, are shown in Tables 1 to 9. The mean age of the participants was 45.7 years. Seven participants were male and the rest were female. The most common cancers between female and male were breast and testis, respectively. None of the subjects in the CPP-ACPF or control group used preventive protocols from their treatment center to prevent chemotherapeutic medication side effects. None of them wore dentures or applied antifungal mouthwash. The evaluated oral signs and symptoms in the participants were mucositis, xerostomia, infection, difficulties in swallowing, dysgeusia, and burning sensation in the mouth, which are shown in Tables 1 to 5. None of these subjects showed signs of infection. Only one subject experienced Grade 3 mucositis on day 21, which was relieved on day 42.

Table 1. Frequency of Xerostomia Status in Control and CPP-ACPF Group in Various Time Periods

Groups	Baseline Xerostomia	Xerostomia After 21 Days	Xerostomia After 42 Days	p-value
Control	50.0%	70.0%	30.0%	0.51
CPP-ACPF	70.0%	30.0%	20.0%	0.86
p-value	0.480	0.1	0.73	

Table 2. Frequency of Dysgeusia Status in Studies Groups in Various Time Periods (%)

Groups	Baseline Dysgeusia	Dysgeusia After 21 Days	Dysgeusia After 42 Days	p-value
Control	40.0%	30.0%	20.0%	0.47
CPP-ACPF	0%	10.0%	.0%	0.36
p-value	0.14	0.48	0.48	

Table 3. Frequency of Burning Sensation Status in Studies Groups in Various Time Periods (%)

Groups	Burning Sensation in Baseline	Burning Sensation After 21 Days	Burning Sensation After 42 Days	p-value
Control	0%	10.0%	20.0%	0.36
CPP-ACPF	20.0%	10.0%	0%	0.36
p-value	0.48	1.00	0.48	

Table 4. Frequency of Difficulties in Swallowing Status in Studies Groups in Various Time Periods (%)

Groups	Difficulties in Swallowing in Baseline	Difficulties in Swallowing After 21 days	Difficulties in Swallowing After 42 Days	p-value
Control	30.0%	30.0%	30.0%	0.36
CPP-ACPF	0%	0.0%	0.0%	0.36
p-value	0.27	0.27	0.27	

Table 5. Frequency of Plaque pH in Studied Groups in Various Time Periods

Groups	Baseline pH			pH After Day 21			pH After 42 Days			p-value
	≤6	6.5	7	≤6	6.5	7	≤6	6.5	7	
Control	0%	60.0%	40.0%	0%	70.0%	30.0%	0%	80.0%	20.0%	0.77
CPP-ACPF	30.0%	40.0%	30.0%	50.0%	20.0%	30.0%	30.0%	40.0%	30.0%	0.96
p-value	0.31			0.19			0.52			

3.2. Numbers analyzed

The results demonstrate that twice-a-day application of CPP-ACPF cannot cause significant changes in the oral status of patients undergoing chemotherapy ($p>0.05$). Table 1 shows the xerostomia status in both groups related to the time of evaluation. Although in the CPP-ACPF paste group, the number of subjects with xerostomia was higher in the beginning of treatment and reduced by passing time; in the control group on day 21, more than half the patients suffered from xerostomia; however, the difference between the two groups was not statistically significant ($p>0.05$).

3.3. Outcomes and estimation

Table 2 shows that subjects experiencing dysgeusia were reduced in the control group, and only one patient experienced dysgeusia on day 21 in the CPP-ACPF group. However, the difference between two groups was not significant ($p>0.05$). Table 3 shows that, the burning sensation occurred in the control group from day 1 to day 42, but it decreased in the CPP-ACPF group during the study; this difference was not significant between the two study groups ($p>0.05$). Table 4 shows that none of the subjects in the CPP-ACPF group had difficulties in swallowing foods, but the control group had problems in every three follow-up sessions, even though the difference was not statistically significant ($p>0.05$). The evaluated salivary conditions including rate of resting and stimulated saliva, buffering capacity, saliva pH, and dental pH plaque, are shown in Tables 5 to 9. The results demonstrate no difference in plaque pH of the two groups ($p>0.05$) (Table 5, 6), but buffering capacity, resting, and stimulated saliva significantly improved in the CPP-ACPF group compared with that of the control group ($p<0.05$). As shown in Tables 7 to 9 at days 21 and 42, patients exhibited a normal condition.

Table 6. Frequency of Saliva pH in Studied Groups in Various Time Periods

Groups	Baseline pH			pH After Day 21			pH After 42 Days			p-value
	Healthy	Mildly acidic	Sever acidic	Healthy	Mildly acidic	Sever acidic	Healthy	Mildly acidic	Sever acidic	
Control	0%	20.0%	80.0%	0%	20.0%	80.0%	0%	20.0%	80.0%	0.66
CPP-ACPF	0%	10.0%	90.0%	0%	0%	100.0%	0%	0%	100.0%	0.13
p-value	0.73			0.43			0.43			

Table 7. Frequency of Buffering Capacity in Studied Groups in Various Time Periods

Groups	Baseline Buffering Capacity			Buffering Capacity After Day 21			Buffering Capacity After 42 Days			p-value
	Very low	Low	Normal	Very low	Low	Normal	Very low	Low	Normal	
Control	30.0%	50.0%	20.0%	30.0%	60.0%	30.0%	30.0%	50.0%	20.0%	0.56
CPP-ACPF	80.0%	10.0%	90.0%	80.0%	20.0%	80.0%	80.0%	10.0%	90.0%	0.50
p-value	0.00			0.00			0.00			

Table 8. Frequency of Resting Saliva Status in Studied Groups in Various Time Periods

Groups	Baseline Resting Saliva Status			Resting Saliva Status After Day 21			Resting Saliva Status After 42 Days			p-value
	Very low	Low	Normal	Very low	Low	Normal	Very low	Low	Normal	
Control	10.0%	60.0%	30.0%	10.0%	60.0%	30.0%	10.0%	50.0%	40.0%	0.81
CPP-ACPF	10.0%	40.0%	50.0%	10.0%	0.0%	90.0%	0.0%	0.0%	100.0%	0.01
p-value	0.53			0.02			0.00			

Table 9. Frequency of Stimulated Saliva Status in Studied Groups in Various Time Periods

Groups	Baseline Stimulated Saliva Status			Stimulated Saliva Status After Day 21			Stimulated Saliva Status After 42 Days			p-value
	Very low	Low	Normal	Very low	Low	Normal	Very low	Low	Normal	
Control	30.0%	50.0%	20.0%	30.0%	60.0%	10.0%	30.0%	50.0%	20.0%	0.81
CPP-ACPF	0.0%	10.0%	90.0%	0.0%	20.0%	80.0%	0.0%	10.0%	90.0%	0.77
p-value	0.004			0.003						

3.4. Harms

The CPP-ACPF paste has no active ingredients that result in sensitivity or toxicity. However, there might be the possibility of sensitivity to the casein that exists in CPP-ACPF paste, which might result in sensitivity for patients who are unable to endure dairy products due to the casein. In this regard, the examiner simply asked patients if they had sensitivity to dairy products containing casein and also applied a small amount of the paste on oral mucosa and evaluated the reaction at the baseline. In this study, none of the patients exhibited sensitivity to the paste.

4. Discussion

The result of this study, which was conducted to evaluate the effect of CPP-ACPF paste on the oral and salivary status of patients undergoing chemotherapy, showed that twice daily application of CPP-ACPF paste can improve resting and stimulated salivary rate and buffering capacity in patients in comparison with those of the control group. There was no significant difference in plaque pH and saliva pH in both groups. Although oral conditions showed improvement in the CPP-ACPF group, the difference between two groups was not significant. This study may be the first in evaluation of the oral and salivary signs and symptoms of patients undergoing chemotherapy with application of a preventive dental material. In this study, various variables have been evaluated. In fact, it could be considered as a pilot study in which other studies could be established according to the results presented here. It is reasonable to benefit from the results of the study until additional studies are completed. Chemotherapy is used as a basic treatment for cancers such as leukemia; surgery and/or radiotherapy are treatments typically used in breast cancer or brain tumors. By using cytotoxic medications in chemotherapy, which are inevitable, the normal cells that reproduce rapidly such as bone marrow, hair, digestive mucosa, and oral cavity tissues will be affected (12), and the oral cavity could experience some tissue changes (13, 14). The side effects of chemotherapy medications usually appear one to two weeks after starting treatment. The destructive effects of these medications are due to their direct cytotoxic effects on the oral cavity's epithelium due to damage to oral cavity mucosa and salivary glands or indirect effects on bone marrow and blood cells, which can cause a compromised immune system, anemia, thrombocytopenia, and increase the risk of infection (15). Oral complications have been seen in 89% of adults being treated for leukemia (11). Xerostomia is one the most common complications caused by these medications due to deficient function of salivary glands. Patients with insufficient saliva may also suffer from increased risk of oral infections, a higher rate of caries, increased dental expenses, and decreased quality of life; therefore, dental treatments and examinations should be done before, during, and after chemotherapy (13).

Results of this study demonstrate that twice-a-day application of CPP-ACPF paste can improve the resting and stimulated salivary rate and buffering capacity in chemotherapy patients. It has been shown that CPP-ACPF paste can increase the buffering capacity of saliva, decrease the demineralization process, and improve re-mineralization up to 63.9% by localizing amorphous calcium phosphate in dental plaque. In addition, the xylitol in this paste and its good taste can stimulate saliva secretion (16). A study conducted at Melbourne University demonstrated that the

CPP-ACPF particles are smaller than 2 nm; thus, they can penetrate into the dental biofilm and increase the CPP concentration in the plaque. It is also bonded to the fluoride and then transports it to the dental plaque. These two agents together increase re-mineralization of the tooth structure and elevate plaque pH. CPP also can degenerate the bacteria and increase saliva pH by producing the ammoniac (17).

In the present study, the positive effects of CPP-ACPF paste have been clearly demonstrated. Knowing the positive and beneficial effects of this component could be useful for patients undergoing chemotherapy to assist them in experiencing less oral complications. In this study, none of the subjects experienced mucositis or infection, so it was not possible to evaluate the effect of the paste on these complications. Many studies have shown that mucositis occurs in patients receiving chemotherapy (13, 14, and 18). The type of the medication may affect this fact. It seems that the prescribed medications in the current study prevented mucositis occurrence, but it is obvious that more studies are necessary to evaluate the effects of chemotherapy agents in oral complications. Unfortunately, no article that assesses the effect of CPP-ACPF components on oral or salivary signs of patients undergoing chemotherapy has been found, and most of the studies focused on the re-mineralization capacity of the paste (8-10). A study by Singh (2009) assessed the effect of calcium-phosphate containing mouthwash in high-risk subjects suffering from xerostomia. In that study, patients who applied this product with fluoride showed less dental caries (19). It seems that fluoride, calcium, and phosphate can decrease the dental caries rate in high caries risk people, but no exact opinion can be given on its effect on oral or salivary status. In our study, the CPP-ACPF group showed better oral conditions in comparison with the control group, but the differences were not statistically significant. More precise evaluation with an increased number of subjects and longer follow-up is needed to show more significant results.

A limitation of this study is that some subjects did not receive their therapy on the follow-up dates, so they were excluded from the study. It was also difficult to persuade patients to cooperate in the study because they had many different types of problems and complications. It is suggested that a similar study on an increased number of subjects and less intervention criteria be conducted.

5. Conclusions

According to the limitations and conditions of the current study, twice-a-day application of CPP-ACPF paste can improve the resting and stimulated salivary rate and buffering capacity of the saliva in patients applying this paste in comparison with those of the control group. Although oral conditions such as burning sensation were improved in the CPP-ACPF group, the difference between the two groups proved insignificant. Also, there was no significant difference in plaque pH and saliva pH in both groups. Findings of this clinical trial proposed that CPP-ACPF paste could result in positive effects on salivary conditions of chemotherapy patients; however, future studies with a higher sample size are suggested.

Acknowledgments:

This clinical trial has been a DDS degree dissertation. The authors sincerely appreciate the endeavors of our statistician Dr. Mohammad Javad Kharrazifard to analyze the data. We are also grateful for the efforts of the anonymous reviewers for their worthwhile comments, which assisted us to improve this paper.

Trial registration: The trial was registered at the U.S. National Institutes of Health (https://www.clinicaltrials.gov) with the identification number NCT01737307.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

References

1) Corti L, Chiarion-Sileni V, Aversa S, Ponzoni A, D'Arcais R, PagnuttiS. Treatment of chemotherapy-induced oral mucositis with light-emitting diode. Photomed Laser Surg. 2006; 24: 207-13. doi: 10.1089/pho.2006.24.207, PMID: 16706701.

2) Lowe O. Pretreatment dental assessment and management of patients undergoing head and neck irradiation. ClinPrev Dent.1988; 8: 24-30.
3) Blom M, Dawidson I, Fernberg JO, Johnson G, Angmar-Månsson B. Acupuncture treatment of patients with radiation-induced xerostomia. Eur J Cancer B Oral Oncol.1996; 32(3):182–90. PMID: 8762876
4) Toth BB, Martin JW, Fleming TJ. Oral complications associated withcancer therapy. J ClinPeriodontol. 1990; 17: 508–15. doi: 10.1111/j.1365-2710.1992.tb01225.x, PMID: 220274.
5) Xelson P, O¨ slund L, Hontwedt M, Paulaner J.The effect of threedifferent mouthrinses on plaqueformation rate and salivary levels of mutans streptococci and lactobacilli. Eur J Dent. 2009; 3(1): 57–61.
6) Rosenthal DI, Lewin JS, Eisbruch A. Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. JClinOncol. 2006; 24: 2636-43. doi: 10.1200/JCO.2006.06.0079, PMID: 16763277.
7) Hay K,Thomson W. Clinical trial of the anticaries efficacy of casein derivatives complexed with calcium phosphate in patients with salivary gland dysfunction. OralSurg Oral Med Oral Pathol Oral RadiolEndod 2002; 93(3) 271-5. doi: 10.1067/moe.2002.120521, PMID: 11925535.
8) Ramalingam L, Messer LB, Reynolds EC. Adding casein phosphopeptide-amorphous calcium phosphate to sports drinks to eliminate in vitro erosion. Pediatr Dent. 2005 Jan-Feb;27(1):61-7. PMID: 15839397
9) Heshmat H, Banava S, Mohammadi E, Kharazifard MJ, Mojtahedzadeh F. The effect of recommending a CPP-ACPF product on salivary and plaque pH levels in orthodontic patients: a randomized cross-over clinical trial. Acta Odontol Scand. 2014 Nov;72(8):903-7. doi: 10.3109/00016357.2014.920515, PMID: 24856191
10) Hegde MN, Moany A. Remineralization of enamel subsurface lesions with casein phosphopeptide-amorphous calcium phosphate: A quantitative energy dispersive X-ray analysis using scanning electron microscopy: An in vitro study. J Conserv Dent. 2012; 15: 61-7. doi: 10.4103/0972-0707.92609, PMID: 22368338, PMCID: PMC3284017.
11) World Health Organization. WHO handbook for reporting results in cancer treatment. Geneva, Switzerland: World Health Organization, 1979: WHO Offset Publication No. 48. Available from: http://whqlibdoc.who.int/offset/WHO_OFFSET_48.pdf
12) Vendrell Ranki. Oral health in cancer therapy. 3rd ed. 2008.
13) Mosalaei A, Nasrolahi H, Shafizad H, Ahmadloo N, Ansari M, Mosleh-Shirazi M, et al. Effect of Oral Zinc Sulphate in Prevention of Radiation Induced Oropharyngeal Mucositis During and After Radiotherapy in Patients with Head and Neck Cancers. MEJC. 2010; 1(2): 69-76
14) Tiemann P, Toelg M, Ramos F MH. Administration of Ratanhia-based herbal oral care products for the prophylaxis of oral mucositis in cancer chemotherapy patients: a clinical trial. Evid Based Complement Alternat Med. 2007 Sep;4(3):361-6. PMID: 17965768, PMCID: PMC1978231
15) Roberts MJ, Messer LB, Reynolds EC. Remineralisation of fluorotic enamel lesions by casein phosphopeptide –amorphous calcium fluorophosphate (CPP-ACFP) solution. IADR-ANZ Division, Abstract 54,2000
16) Carl W. Xerostomia Management in the Head and Neck Radiation Patient, Texas dental journal. 2004; 121(6): 483-97.
17) Mayne RJ, Cochrane N, Cai F, Woods M, Reynolds E. In-vitro study of the effect of casein phosphopeptide amorphous calcium fluoride phosphate on iatrogenic damage to enamel during orthodontic adhesive removal. Am J Orthod Dentofacial Orthop. 2011; 139(6): 543-51. doi: 10.1016/j.ajodo.2010.09.027, PMID: 21640866
18) Douglas E. Peterson, James B. Jones, Robert G. Randomized, Placebo-Controlled Trial of Saforis for Prevention and Treatment of Oral Mucositis in Breast Cancer Patients Receiving Anthracycline-Based chemotherapy. Cancer. 2007; 109(2): 322–331
19) Singh ML, Papas AS. Long-term clinical observation of dental caries in salivary hypofunction patients using a supersaturated calcium-phosphate remineralizing rinse. J Clin Dent. 2009;20 (3):87-92. PMID: 19711609