

Use of Curcumin in Radiochemotherapy Induced Oral Mucositis Patients: A Control Trial Study

Shivayogi Charantimath

I. INTRODUCTION

Abstract—Radiotherapy and chemotherapy are effective for treating malignancies but are associated with side effects like oral mucositis. Chlorhexidine gluconate is one of the most commonly used mouthwash in prevention of signs and symptoms of mucositis. Evidence shows that chlorhexidine gluconate has side effects in terms of colonization of bacteria, bad breath and less healing properties. Thus, it is essential to find a suitable alternative therapy which is more effective with minimal side effects. Curcumin, an extract of turmeric is gradually being studied for its wide-ranging therapeutic properties such as antioxidant, analgesic, anti-inflammatory, antitumor, antimicrobial, antiseptic, chemo sensitizing and radio sensitizing properties. The present study was conducted to evaluate the efficacy and safety of topical curcumin gel on radiochemotherapy induced oral mucositis in cancer patients. The aim of the study is to evaluate the efficacy and safety of curcumin gel in the management of oral mucositis in cancer patients undergoing radio chemotherapy and compare with chlorhexidine. The study was conducted in K.L.E. Society's Belgaum cancer hospital. 40 oral cancer patients undergoing the radiochemotherapy with oral mucositis was selected and randomly divided into two groups of 20 each. The study group A [20 patients] was advised Cure next gel for 2 weeks. The control group B [20 patients] was advised chlorhexidine gel for 2 weeks. The NRS, Oral Mucositis Assessment scale and WHO mucositis scale were used to determine the grading. The results obtained were calculated by using SPSS 20 software. The comparison of grading was done by applying Mann-Whitney U test and intergroup comparison was calculated by Wilcoxon matched pairs test. The NRS scores observed from baseline to 1st and 2nd week follow up in both the group showed significant difference. The percentage of change in erythema in respect to group A was 63.3% for first week and for second week, changes were 100.0% with $p = 0.0003$. The changes in Group A in respect to erythema was 34.6% for 1st week and 57.7% in second week. The intergroup comparison was significant with p value of 0.0048 and 0.0006 in relation to group A and group B respectively. The size of the ulcer score was measured which showed 35.5% [$P=0.0010$] of change in Group A for 1st and 2nd week showed totally reduction i.e. 103.4% [$P=0.0001$]. Group B showed 24.7% change from baseline to 1st week and 53.6% for 2nd week follow up. The intergroup comparison with Wilcoxon matched pair test was significant with $p=0.0001$ in group A. The result obtained by WHO mucositis score in respect to group A shows 29.6% [$p=0.0004$] change in first week and 75.0% [$p=0.0180$] change in second week which is highly significant in comparison to group B. Group B showed minimum changes i.e. 20.1% in 1st week and 33.3% in 2nd week. The p value with Wilcoxon was significant with 0.0025 in Group A for 1st week follow up and 0.000 for 2nd week follow up. Curcumin gel appears to an effective and safer alternative to chlorhexidine gel in treatment of oral mucositis.

Keywords—Cur cumin, chemotherapy, mucositis, radiotherapy.

Shivayogi Charantimath is Reader Department of oral medicine and radiology with the K.L.E.V.K. Institute of Dental sciences, K.L.E. University, Belgaum, Karnataka, India (e- mail: yogi031_shiv@rediffmailcom).

ORAL mucositis is a common cause of cancer therapies due to multicycle chemotherapy and radiotherapy with or without concurrent chemotherapy of head and neck cancer. This disparity is related to complex risk assessment of multifactorial patient and treatment factors and different techniques of rating mucositis. [1]. Cytotoxic radiotherapy and chemotherapy or both are becoming increasingly effective for treating malignancies but they are associated with long and short term side effects. The disruption in the function and integrity of the oral cavity is among the clinically important side effects which is acute in nature and may manifest as severe ulceration (mucositis) and fungal infection of the mouth (oral candidiasis, thrush) [2]. These disease and treatment induced complications may lead to life threatening infection such as septicemia in some cases.

Current treatment modalities include use of chlorhexidine gluconate mouth wash used in prevention and amelioration of signs and symptoms of both chemotherapy and radiotherapy induced mucositis. However, chlorhexidine mouth wash possesses potential side effects due to the amount of stinging, dehydration, which might lead to microbial colonization over the affected mucosa and further complicate the patients' condition [2], [3]. Also, previously performed study indicates that alcohol containing mouth rinses cause more patient pain than those without alcohol [4], [5]. Thus, it is essential to find a suitable alternative which is more efficacious with minimal side effects. Cur cumin, an extract of turmeric is progressively being studied for its varied therapeutic properties such as antioxidant, analgesic, anti-inflammatory, antitumor, antimicrobial, antiseptic, chemo sensitizing and radio sensitizing properties. [6], [7].

The anti-inflammatory properties of curcumin may be attributed to its ability to inhibit both biosynthesis of inflammatory prostaglandins which further blocks cyclooxygenase and lipoxigenase activity, thereby inhibiting prostaglandins leukotriene release and neutrophil function during inflammatory states [8], [9]. The present study was conducted to evaluate the efficacy and safety of topical curcumin in reducing the severity of signs and symptoms of radio chemotherapy induced oral mucositis in cancer patients and compare with chlorhexidine.

II. AIM OF THE STUDY

To evaluate the efficacy and safety of curcumin in the management of oral mucositis in cancer patients undergoing radio chemotherapy.

III. OBJECTIVES OF THE STUDY

1. To evaluate the efficacy of curcumin in management of oral mucositis.
2. To compare the efficacy of curcumin gel with chlorhexidine gel in management of oral mucositis.

IV. MATERIALS AND METHODS

The study was conducted in K.L.E. Cancer hospital for a period of 3 months following the ethical approval from the institution review board. 40 patients with oral cancer of either sex undergoing the radio chemotherapy, clinically diagnosed with oral mucositis was selected and randomly divided into two groups.

V. METHOD OF COLLECTION OF DATA

Patients were briefed about the study and signed informed consent was obtained. Detailed case history was recorded and intra oral examination was performed on the patients. The cycles of radiotherapy and chemotherapy was recorded. 40 patients with clinically diagnosed mucositis were selected for the study based on inclusion and exclusion criteria. They were randomly assigned into two groups, namely the Study and Control groups consisting of twenty patients each. Patients willing to participate in the study were included and patients who were terminally ill, using any prophylactic or therapeutic mouthwashes or those unable to comply with curcumin mouth wash as judged by the patient himself or investigator were excluded.

Study Tool

Patients were advised to apply the gel three times a day on each ulcer after meals and not to consume food or water for half an hour after application of the gel. All patients were provided with same measuring applicator and were instructed about the quantity and method of gel application on the first appointment itself. The patients with clinically diagnosed oral mucositis were graded using Numerical Rating Scale (NRS), oral mucositis assessment scale and WHO mucositis scale. Pre-treatment and post-treatment grading was recorded.

Assessment of efficacy of gel was done on the basis of time required for regression in pain, Erythema and size of the ulcer.

- Details of curcumin gel: Contents Cure next oral gel (Abbott Pharmaceuticals). Per gram of gel contained 10 mg of *Curcuma longa* extract.
- Details of hexigel: chlorhexidine gluconate 1.0%

Statistical Analysis

Data obtained was analyzed using SPSS software version 20. Our study comprised of 37 male and 3 female patients. Most of the patients were diagnose with buccal mucosa cancer. The standard deviation and mean was calculated for 3 scales and comparison between two groups was calculated by Mann-Whitney U test.

TABLE I
MUCOSITIS ASSESSMENT SCALE [2]-[10]

Numerical Rating Scale (Nrs)	Oral Mucositis Assessment Scale (OMAS).	WHO Mucositis scale
0=no pain and 10=worst possible pain	Erythema Grade 0 = normal, Grade 1= not severe, Grade 2 = severe The score for ulcerations was based on area of ulceration ranging from 0 to 3 [10]: Grade 0= normal, Grade 1 = Less than 1 cm Grade 2 = between 1-3 cm ² , Grade 3 = 3 cm ²	Grade 0: No changes. Grade 1: Soreness / (+) erythema. Grade 2: Erythema (++), Ulcer, can eat food. (Erythema with ulcers less than 1 cm) Grade 3: Ulcer (+++), (erythema with ulcers more than 1cms) require liquid food. Grade 4: Ulcer with hemorrhage and necrosis, alimention not possible.

VI. RESULTS AND OBSERVATIONS

The results obtained were compared by Mann-Whitney U from Group A and Group B with respect to baseline, 1st week and 2nd week NRS, Erythma, size of the Ulcer and WHO Mucositis assessment scale. In respect of NRS scale there was reduction in pain in both groups with 41.3%, [p=0.0098], 18.2%, [p=0.0002] Group A and Group B respectively. Intergroup comparison was calculated by Wilcoxon matched pairs test where the result was statistically significant with p value of 0.0001 as shown in Table II, Fig 1.

Comparison of Group A and Group B with respect to baseline, 1st week and 2nd week erythema scores by Mann-Whitney U test when applied showed significant difference was observed 63.3% of change was noted in group A for 1st week [p=0.0003] and second follow up was 100.0% change in erythema [p=0.0003]. The Group B results were 34.6%, of changes in 1st week [p=0.0077], and changes in second week was 57.7%, [p=0.0022*]. The intergroup comparison with Wilcoxon matched pair obtained was p value of 0.0048*which is statistically significant [Table III, Fig. 2].

The result observed in terms of percentage of change in size of ulcer in Group A was 35.5% for 1 week [p=0.0010*] follow up and second week follow up changes was 103.4%, [p=0.0003]. The percentage of changes in group B was 24.7%, [p=0.9999] for first follow up and 53.6% of changes was observed at second follow up [p=0.1088] which is statistically significant. Wilcoxon matched pairs test was applied for intergroup comparison. There was significant difference between two groups with p value of .0001 [Table IV], [Fig. 3].

The results observed in comparison of Group A and Group B with respect to baseline, 1 week and 2 week WHO scores by Mann-Whitney U test are percentage of change in Group A was 29.6% of change was noted [p=0.0004]. The percentage of change in second follow up was 75%, [p=0.0003]. This reading is statistically significant. The percentage of change in Group B was 20.1% [p=0.0180*] for first follow up and 33.3% of change in second follow up [p=0.0003*] which is statistically significant. Intergroup comparison of grading results was significant with p value of 0.0025* first follow up and 0.0001* for Second follow up by Wilcoxon on matched paired test, which is statistically significant [Table V], [Fig. 4].

TABLE II
COMPARISON OF GROUP A AND GROUP B WITH RESPECT TO BASELINE, 1 WEEK AND 2 WEEK NRS SCORES

Groups	Baseline			1 week			2 week			Change from Baseline to 1 week			Change from Baseline to 2 week		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Group A	6.12	0.99	6.00	3.59	0.80	4.00	1.94	0.90	2.00	2.53	0.94	2.00	4.18	1.13	4.00
Group B	6.11	0.90	6.00	5.00	0.91	5.00	4.22	1.11	4.00	1.11	0.32	1.00	1.89	0.68	2.00
% of change in A													41.3%#	p=0.0098*	68.3%#
% of change in B													18.2%#	p=0.0002*	30.9%#
Z-value		-0.0660			-3.7626			-4.3897			-4.6537			-4.6372	
P-value		0.9474			0.0002*			0.0001*			0.0001*			0.0001*	

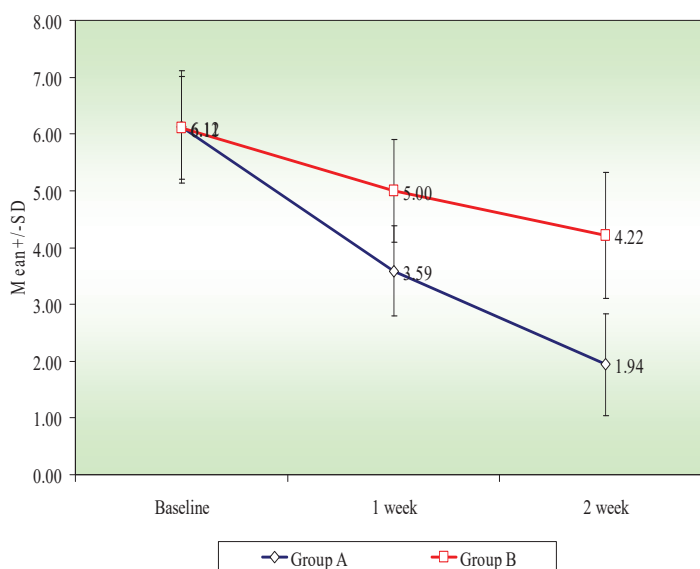


Fig. 1 Comparison of group A and group B with respect to baseline, 1 week and 2 week NRS scores

TABLE III
COMPARISON OF GROUP A AND GROUP B WITH RESPECT TO BASELINE, 1 WEEK AND 2 WEEK ERYTHEMA SCORES

Groups	Baseline			1 week			2 week			Change from Baseline to 1 week			Change from Baseline to 2 week		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Group A	1.76	0.44	2.00	0.65	0.49	1.00	0.00	0.00	0.00	1.12	0.33	1.00	1.76	1.13	0.44
Group B	1.44	0.51	1.00	0.94	0.42	1.00	0.61	0.50	1.00	0.50	0.51	0.50	0.83	0.68	0.71
% of change in A													63.3%#	p=0.0003*	100.0%#
% of change in B													34.6%#	p=0.0077*	57.7%#
Z-value		-1.6172			-1.4027			-3.0860			-2.8219			-3.4160	
P-value		0.1058			0.1607			0.0020*			0.0048*			0.0006*	

TABLE IV
COMPARISON OF GROUP A AND GROUP B WITH RESPECT TO BASELINE, 1 WEEK AND 2 WEEK ULCER SCORES BY MANN-WHITNEY U TEST

Groups	Baseline			1 week			2 week			Change from Baseline to 1 week			Change from Baseline to 2 week		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Group A	1.71	0.59	0.82	0.53	0.06	0.24	0.88	0.49	1.65	0.61	0.33	1.00	1.76	1.13	0.44
Group B	1.56	0.62	1.56	0.62	1.39	0.61	0.00	0.00	0.17	0.38	0.51	0.00	0.83	0.68	0.71
% of change in A													35.5%#	p=0.0010*	103.4%#
% of change in B													24.7%#	p=0.9999	53.6%#
Z-value		-0.7096			-2.8384			-4.8517			-4.1586			-4.7032	
P-value		0.4780			0.0045*			0.0001*			0.0001*			0.0001*	

*p<0.05, # applied Wilcoxon matched pairs test

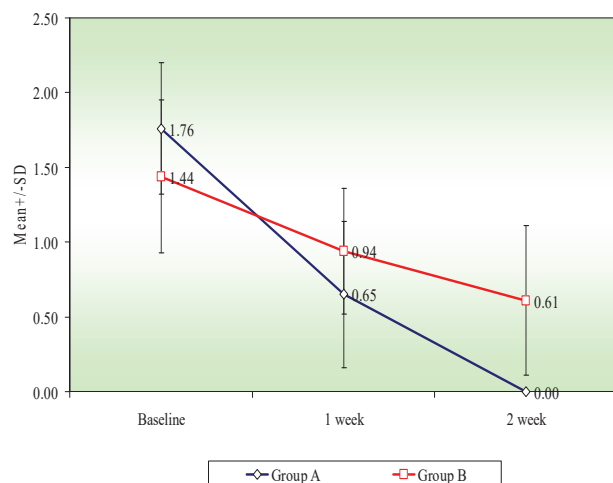


Fig. 2 Comparison of group A and group B with respect to baseline, 1week and 2 week ERYTHMA scores

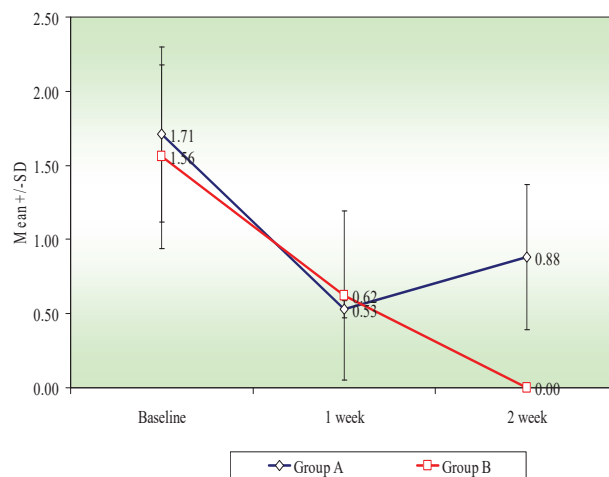


Fig. 3 Comparison of group A and group B with respect to baseline, 1week and 2 week ULCER scores

TABLE V
COMPARISON OF GROUP A AND GROUP B WITH RESPECT TO BASELINE, 1WEEK AND 2 WEEK WHO SCORES BY MANN-WHITNEY U TEST

Groups	Baseline			1 week			2 week			Change from Baseline to 1 week			Change from Baseline to 2 week		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Group A	2.35	0.79	1.29	0.69	0.47	0.51	1.06	0.43	1.88	0.70	0.33	1.00	1.76	1.13	0.44
Group B	2.50	0.51	2.11	0.83	1.89	0.83	0.39	0.50	0.61	0.50	0.51	0.00	0.83	0.68	0.71
% of change in A										29.6%#, p=0.0004*			75.0%#, p=0.0003*		
% of change in B										20.1%#, p=0.0180*			33.3%#, p=0.0003*		
Z-value	-0.2970			-2.5414			-4.1256			-3.0199			-4.1421		
P-value	0.7664			0.0110*			0.0001*			0.0025*			0.0001*		

*p<0.05, # applied Wilcoxon matched pairs test

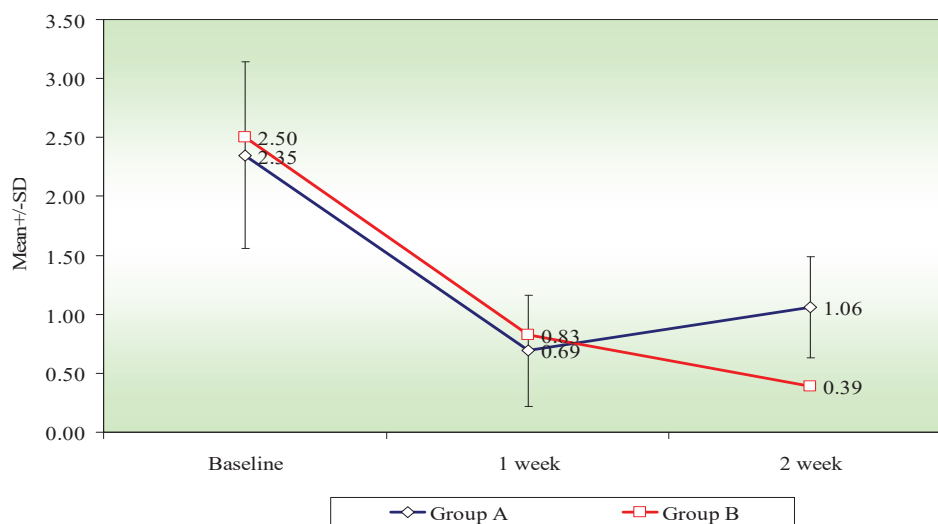


Fig. 4 Comparison of group A and group B with respect to baseline, 1week and 2 week WHO scores

VII. DISCUSSION

The present study was conducted to evaluate the efficacy of curcumin gel in oral mucositis induced by radio-chemotherapy. The study comprised of 40 subjects. 20 patients were treated with cure next and 20 patients with hexigel. All the patients were graded by NRS, OMAS, and

WHO Mucositis scale. There was significant difference in improvement with patients with curcumin application.as shown in results and observation. The potential adverse effects from the treatment for HNSCC are numerous. Radical surgery can result in disfigurement & functional impairment, but even the organ-preserving treatment methods of radiation and

chemotherapy may result in a host of negative side effects, some permanent [1]. Common side effects of radiotherapy include mucositis, oral candidiasis, loss of taste and xerostomia, which may be permanent due to the damaging effect of radiation on the salivary glands [2]. Osteoradionecrosis of bones within the radiation field (most commonly the mandible) may occur as a result of damage to the bone vasculature and osteocytes and is one of the most serious complications of radiotherapy. Oral mucositis, also called stomatitis, is a common, debilitating complication of cancer chemotherapy and radiotherapy, occurring in about 40% of patients. It results from the systemic effects of cytotoxic chemotherapy agents and from the local effects of radiation to the oral mucosa. Oral mucositis is inflammation of the mucosa of the mouth which ranges from redness to severe ulceration. Symptoms of mucositis vary from pain and discomfort to an inability to tolerate food or fluids. Mucositis may also limit the patient's ability to tolerate either chemotherapy or radiotherapy. Mucositis may be so severe as to delay treatment and so limit the effectiveness of cancer therapy. Patients with damaged oral mucosa and reduced immunity resulting from chemotherapy and radiotherapy are also prone to opportunistic infections in the mouth. The mucositis may affect patients' gum and dental condition, speech and self-esteem are reduced, further compromising patients' response to treatment and/or palliative care. It is therefore extremely important that mucositis be prevented whenever possible, or at least treated to reduce its severity and possible complications.

Currently, there is a bewildering number of interventions to choose from, but no high quality synthesis of the best research evidence for these interventions best practices

Chlorhexidine gluconate is one of the most commonly used mouthwash solutions identified in studies and has been used in prevention and amelioration of signs and symptoms of both chemotherapy and radiotherapy induced mucositis. due to the amount of stinging and dehydration it can cause which might lead to microbial colonization over the affected mucosa and further complicate the patients' condition. Also, previously performed study indicates that alcohol containing mouth rinses cause more patient pain than those without alcohol. Thus, it is essential to find a suitable alternative which is more efficacious with minimal side effects.

Phytochemicals have greatly attracted the attention of researchers in the field of medicine. Curcumin, an extract of turmeric is progressively being studied for its varied therapeutic properties such as antioxidant, analgesic, anti-inflammatory, antitumor, antimicrobial, antiseptic, chemo sensitizing and radio sensitizing properties. The present study was conducted to evaluate the efficacy and safety of topical curcumin in reducing the severity of signs and symptoms of radio-chemotherapy induced oral mucositis in cancer patients.

Curcumin (diferuloylmethane) is a polyphenol derived from the *Curcuma longa* plant, commonly known as turmeric. Curcumin has been used extensively in Ayurvedic medicine for centuries, as it is nontoxic and has a variety of therapeutic properties including anti-oxidant, analgesic, anti-inflammatory

and antiseptic activity. More recently curcumin has been found to possess anti-cancer activities via its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis and metastasis. Curcumin has shown anti-proliferative effect in multiple cancers, and is an inhibitor of the transcription factor NF- κ B and downstream gene products (including c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF- α , interleukins and MMP-9). In addition, curcumin affects a variety of growth factor receptors and cell adhesion molecules involved in tumor growth, angiogenesis and metastasis. [6]-[7]-[9].

The oral mucosa has an environment rich in microbes such as bacteria, fungi, and viruses. The presence of disruptions provides an important portal of entry for these infectious organisms within the mucosal lining, especially in cancer patients suffering from neutropenia. The importance of mucositis as a risk factor for bacteremia and sepsis is also well established. These factors lead to break from radio-chemotherapy and under treatment resulting in suboptimal cancer therapy [11], [12].

For patients receiving fractionated radiation or chemo radiation for cancers of the head and neck, adverse mucosal changes become apparent at cumulative radiation doses as low as 10 Gy. In almost all cases, ulceration is seen by 30 Gy (the end of the third week of treatment) [13].

Chlorhexidine gluconate is a widely used drug in dentistry, which forms a protective barrier over the damaged mucosa consisting of a whitish membrane that results from the coagulation of serum and salivary proteins, thus reducing the severity of oral ulcerations. In view of this property, various studies were performed by several investigators to assess the efficacy of chlorhexidine in management [14].

Karthekaye Patil conducted a study on efficacy of curcumin 0.4% mouth wash on 10 patients receiving radiotherapy and chemotherapy and compared with chlorhexidine mouth wash. he concluded that burning sensation and ulcer reduced significantly in patients who used curcumin mouth wash. Our study also had similar findings. There was significant difference in all the scale measured [15].

Dr Radha and Dr Anjana Bagewadi compared effectiveness of curcumin with triamcelone acetonide in the gel form in treatment of minor recurrent aphthous stomatitis. the result showed significant difference in size, pain, number and dimension of ulcer in group 1 and group 2 within 7 days. These findings are in consistent to our study results [16].

Aggarwal reported that curcumin has the potential to inhibit NF- κ B. The expression of several genes that are regulated by NF- κ B has also shown to be suppressed by curcumin. These include cell surface adhesion molecules, chemokines, TNF, MMP9, COX2 & NOS. Since these genes are critical regulators of inflammation, the suppression of expression of these genes explains the anti-inflammatory effects of curcumin [17].

Land et al., performed a study on Role of curcumin and the inhibition of NF- κ B in the onset of methotrexate-induced mucosal barrier injury in intestinal mucosa of rats and

concluded that inhibition of NF- κ B does not increase intestinal side effects of the anticancer treatment, suggesting a safe use of curcumin and caffeic acid phenethyl ester (CAPE) in combination with anticancer treatment [18].

Elad et al. performed a pilot study on 7 pediatric patients receiving chemotherapy to evaluate the efficacy of curcumin oil in controlling the signs and symptoms of oral mucositis and concluded that curcumin mouthwash is well tolerated and efficacious [19].

The therapeutic properties of curcumin in terms of inhibition of growth of various bacteria, fungi and parasites were reviewed by Nagpal et al. and they concluded that curcumin was effective against such microbes. It was observed that following one-week application of curcumin, the lesions of guinea pigs infected with dermatophyte and fungi showed improvement [8].

VIII. CONCLUSION

The present study provides strong evidence that curcumin gel can be used as an effective and safer alternative to hexigel in treatment of oral mucositis. Statistically significant difference was found between the Study and Control groups in morbidity associated with Radio-chemotherapy induced OM patients. Curcumin was found to be better than chlorhexidine gel in terms of rapid healing of wound and better patient compliance in management of radio-chemotherapy induced oral mucositis. No oral or systemic complications were reported.

ACKNOWLEDGEMENT

Sincere thanks to Dr Sachin, and staff of K.L.E. Society Cancer Hospital Belagavi for permitting to carryout study in hospital.

REFERENCES

- [1] Reason Wilken, Mysore S Veena, arilene B Wang and Eri S Srivatsan Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma Molecular Cancer 2011.
- [2] Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, et al. Interventions for preventing oral mucositis for patients with cancer receiving treatment (Review). *The Cochrane Library*. 2013; 2:1-263.
- [3] Bensinger W, Schubert M, Ang KK, Brizel D; Brown E, Eilers JG, et al. NCCN task force report: prevention and management of mucositis in cancer care. *Journal of the National Comprehensive Cancer Network*. 2008;6(1): S1-24.
- [4] Barasch A, Elad S, Altman A, Damato K, Epstein J. Antimicrobials, mucosal coating agents, anesthetics, analgesics, and nutritional supplements for alimentary tract mucositis. *Support Care Cancer*. 2006; 14: 528-32.
- [5] Hodgkinson B, Long L, Evans D. Prevention and treatment of oral mucositis in cancer patients. *Best Practice*. 1998;2(3):1-6.
- [6] Sharmila Devi, Prsanna Neelkantan Curcumin- Pharmacological Actions and Its Role in Dentistry Asian J Pharmaceut Res Health Care: 6: 119-22.
- [7] Chaturvedi TP. Uses of turmeric in dentistry: An update. *Indian J Dent Res*. 2009;20 (1): 107-09.
- [8] Nagpal M, Sood S. Role of curcumin in systemic and oral health. *Journal of Natural Science, Biology and Medicine*. 2013;4(1):3-7.
- [9] Mimeault M, Batra SK. Potential applications of curcumin and its novel synthetic analogs and nanotechnology-based formulations in cancer prevention and therapy. *Chinese Medicine*. 2011;6(31):1-19
- [10] Bensinger W, Schubert M, Ang KK, Brizel D; Brown E, Eilers JG, et al. NCCN task force report: prevention and management of mucositis in cancer care. *Journal of the National Comprehensive Cancer Network*. 2008;6(1): S1-24.
- [11] Sonis ST. Pathobiology of Oral Mucositis: novel insights and opportunities. *J Support Oncol*. 2007; 5: 3-11.
- [12] Ferretti GA, Raybould TP, Brown AT, Macdonald JS, Greenwood M, Maruyama Y, et al. Chlorhexidine prophylaxis for chemotherapy- and radiotherapy-induced stomatitis: a randomized double-blind trial. *Oral Surg Oral Med Oral Pathol*. 1990;69: 331-38.
- [13] Soares AF, Aquino ARL, Carvalho CHP, Nonaka CFW, Almeida D, Pinto P. Frequency of oral mucositis and microbiological analysis in children with acute lymphoblastic leukemia treated with 0.12% Chlorhexidine gluconate. *Braz Dent J*. 2011;22 (4):312-16.
- [14] Foote RL, Loprinzi CL, Frank AR, O'Fallon JR, Gulavita S, Tewfik HH, et al. Randomized trial of a chlorhexidine mouthwash for alleviation of radiation induced mucositis. *J Clin Oncol*. 1994;12: 2630-33.
- [15] Karthekey Patil, Mahimaa Guled Gud, Pk Kulkarni, Deepika Keshari, Shristi Tayal Use of Curcumin Mouth Rine in Radio-Chemotherapy Induces Oral Mucositis: A Pilot Study. *Journal of Clinical and Diagnostic Research*. 2015 Aug, 9(8): ZC59-ZC62.
- [16] Dr Radha, Dr Anjana Bagewadi Comparison of effectiveness of curcumin with triamcinolone acetonide in the gel form in treatment of minor recurrent aphthous stomatitis: A randomized clinical trial *J Pharma Invest* 2014 July -Sept;4(3):138-147.
- [17] Aggarwal, et al. Anticancer potential of curcumin (Review). *Anticancer Research*. 2003;23: 363-98.
- [18] Land B, Blijlevens NMA, Martijn J, Timal S, Donnelly JP, Witte TJM, et al. Role of curcumin and the inhibition of NF- κ B in the onset of chemotherapy-induced mucosal barrier injury. *Leukemia*. 2004; 18: 276-84.
- [19] Elad S, Meidan I, Sellam G, et al. Topical curcumin for the prevention of oral mucositis in paediatric patients: case series. *Altern Ther Health Med*. 2013;19(3):21-24.