Original Article

DOI: 10.7860/JCDR/2017/23975.9571

Dentistry Section

A Randomized Placebo- Controlled Double Blind Clinical Trial of Quercetin in the Prevention and Treatment of Chemotherapy-Induced Oral Mucositis

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ABSTRACT

Introduction: Oral Mucositis (OM) is a serious complication of chemotherapy that results in painful debilitating inflammation that sometimes ends in interruption of treatment.

Aim: The study evaluated the effect of quercetin (a natural flavonoid) on preventing and treating chemotherapy induced OM in patients with blood malignancies.

Materials and Methods: This double-blind, placebo controlled randomized trial was carried out on 20 adult patients who underwent high dose chemotherapy for blood malignancies. Patients were divided into two groups (10 patients in the intervention group and 10 patients in the control group). Patients in the intervention group were administered 250 mg quercetin capsules twice daily for four weeks.

Results: Nine out of 20 patients developed OM (three in the intervention group and six in the control group). The incidence of OM was lower in the intervention group although it was not statistically significant (p=0.189). The mean severity of OM was higher in the intervention group (2.6 vs 2). Healing time, age, gender, type of malignancy, drug type and duration of OM were not different in two groups.

Conclusion: The incidence of mucositis was lower in the quercetin group, but mucositis was more severe in the intervention group, which may be due to lower oral health status in the intervention group.

Keywords: Cancer, Flavonoids, Haematologic malignancies

INTRODUCTION

Oral Mucositis (OM), a complication of cancer treatment, is a debilitating disorder and is defined as an injury of the oral mucosa in patients with cancer, induced by chemotherapy or radiation to the head and neck region [1].

A very complicated biologic process is responsible for OM. Mechanisms such as direct injury to the oral epithelium during cell proliferation, dysregulation of the immune system, exaggerated inflammatory responses, changes in inflammatory cytokines {e.g., Tumour Necrosis Factor-α (TNF-α), Interleukin-1 (IL-1), and interleukin 6 (IL-6)}, and super infections by oral bacterial flora are involved in OM [2,3].

In some cases, OM has a dose limiting toxicity, delaying or preventing continuing of chemotherapy that may potentially have an important effect on survival or cure. Chemotherapy induced OM is typically less severe and is of shorter duration (3–12 days) than that associated with Radiotherapy (RT) (3–12 weeks) and usually affects non-keratinized mucosa, in the first and second weeks of chemotherapy treatment, and subsides during the third or fourth week following chemotherapy [2,4].

Sodium carbonate, local anaesthetics such as diphenhydramine and promethazine mixed with manganese milk, chlorhexidine and saline mouthwashes have been used to control OM in addition to covering agents such as sucralfate, and an anti-inflammatory agents (e.g., chamomile) or local steroids [5-11]. A systematic review revealed that a low level laser has beneficial effects over a range of wavelengths and intensities in managing OM in patients with cancer [12]. Other systematic reviews have shown useful effects by using cryotherapy, cytokines, growth factors, honey, aloevera, amifostin, glutamine, and antibiotic pastille in different types of cancer and treatment settings [13-17].

Quercetin belongs to the flavonoid family and is the most available type of flavonoids for daily diet and has the most antioxidant and anti-inflammatory activity among available flavonoids. The anti-inflammatory properties have been related to restriction of cytokines including IL-12, INF-γ, INF-α, IL-8, cyclo-oxygenase 2, and prostaglandin E. Furthermore, quercetin produces an antioxidant effect by inhibiting free radicals and nitric oxide [18-22]. Topical quercetin has been used to treat oral aphthous stomatitis, and complete improvement of lesions has been reported [23]. In vitro and animal studies and trials on healthy volunteers have suggested use of quercetin in various situations such as drug resistant diseases related to oxidative stress, blood pressure, inhibition of cancer cell cycle progression, and cardio-metabolic risk [24-28]. A critical review supported the safety of quercetin for addition to food as a supplement [29]. In a study conducted by the authors, systemic administration of quercetin in oral lichen planus had no considerable clinical benefit [30].

Due to the anti-inflammatory and antioxidant properties of quercetin, it may prevent or treat OM. This study assessed the efficacy of quercetin in preventing and treating chemotherapy induced oral mucositis in haematologic malignancies.

MATERIALS AND METHODS

Patients

The study was conducted in the Department of Heamatology Imam Reza Hospital, Mashhad, Iran, from January 2010 to January 2012. Twenty-three patients who underwent chemotherapy for blood malignancies (for the first time) participated in this double blind, placebo controlled randomized trial.

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Iran), and all subjects gave written

informed consent to participate in the study. This study was registered in the U.S. National Institute of Health Registry of Clinical Trials (registry number NCT01732393). The inclusion criteria were: (a) 15 years of age or older; (b) patient undergoing chemotherapy for a haematologic malignancy; (c) the haematologist approved the patient's participation; and (d) agreement of patient to participate in the trial. Exclusion criteria were: (a) presence of any oral lesion at the beginning of the trial; (b) loss of follow up; (c) use of digoxin and cyclosporine; and (d) patient death. There were no patients with history of previous head and neck surgery, pregnancy, and previous or simultaneous radiotherapy. No patients had dentures.

Sample Size

This study was the first research on OM and quercetin, so we enrolled 23 patients in this pilot study.

Intervention, Randomization, and Blinding

The patients were randomly allocated into two groups (quercetin and placebo) according to a series of random numbers created by a calculator. Eleven patients were in the intervention group, and 12 patients in the control group. All patients were followed until the end of chemotherapy treatment and were informed about oral hygiene, including drinking water and brushing teeth with a soft tooth brush presoaked in warm water, after each meal, as well as abstinence from alcohol, smoking cigarettes, hot or cold drinks, and very spicy, acidic, and tough foods during chemotherapy. If a patient had severe thrombocytopenia (<50,000/mm^3) during chemotherapy that might challenge efficient brushing, other less aggressive oral health measures was taught to the patient.

The two study groups were provided identical capsules (series A and B). The intervention group received A capsules containing 250 mg quercetin hydrate (Sigma–Aldrich Co; St Louis, MO, USA) two times a day, and the control group received B capsules (placebo) containing a lactose capsule. Drug therapy was initiated at the onset of chemotherapy. In both the groups patients received the drugs for a period of four weeks. The patients, researcher, and statistician were blind to the content of the capsules, and only the pharmacologist (HO) was aware.

Evaluation of Outcomes

Patients' oral health was checked by an oral medicine specialist before chemotherapy was initiated. A dentist and an oral medicine specialist who were blinded to the randomization and treatment monitored patients for the appearance of OM daily until the end of chemotherapy. Patients were examined with an overhead light, by using dental tools and mirrors. Sterile gauze was used to wipe out debris when necessary. The World Health Organization (WHO) oral toxicity scale was used to evaluate OM. [Table/Fig-1] summarizes the WHO scale for assessing OM [31].

The primary outcome of the study was preventing incidence and onset of OM. The secondary outcome was the severity of OM based on WHO scale.

Although rare, any adverse effect in the patients was recorded and kept under observation. If the adverse event was too serious, the trial was stopped, and the patient was closely monitored.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS 11.0 (SPSS 11.0 windows, SPSS Inc, Chicago, IL, USA). The Mann-Whitney U test evaluated mucositis intensity. The Friedman test evaluated the effect of time. A p-value was considered significant at the 0.05 level for the Mann-Whitney U test. To prevent a repeated measurement error, we divided α into 10 and 0.05 for the Friedman and Mann-Whitney U test.

RESULTS

Twenty-three patients were included in this trial. One patient died (in the control group) and 2 patients were discharged (1 in each group) before the trial ended; thus, 20 patients completed the trial. In each group, four women and six men received either quercetin or placebo [Table/Fig-2].

The mean age of patients was 33±15.9 (cases: 33±17, controls: 33±16), and the patients ranged from 15 to 5-year-old. There was no significant difference between the two groups (p =0.946) [Table/Fig-3]. Patients received different chemotherapy regimens [Table/Fig-4]. Cytarabin and daunorubicin was the most common regimen. The type of chemotherapy regimen was not related to incidence of mucositis in the study population (p =0.685).

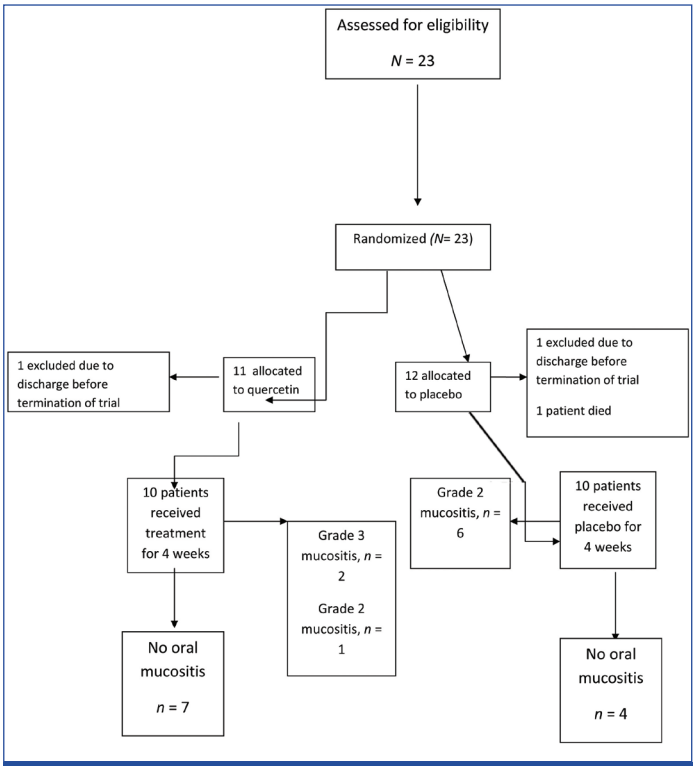
Three patients in the intervention group were affected by OM. Two patients had Grade 3 OM, and one had Grade 2 OM. The mean severity of OM was 0.8±1.30 in the intervention group. In the control group, six patients were involved, and all had Grade 2 OM. The mean severity of OM was 1.30±1.16 in the control group. No patients had Grade 4 OM. [Table/Fig-5] shows the mean severity of mucositis in the two groups and the total study population. Incidence of mucositis was lower in the intervention group (30% vs 60%).

Although, fewer patients had mucositis in the intervention group, the mucositis was more severe in this group (2.6) compared to the control group (2) but was not statistically different (p =.12). [Table/Fig-3] shows detailed findings of the study. An interesting finding in these three patients was the poor oral health level due to the severity of the systemic disease. Onset of mucositis was different from 8 to 11 days after chemotherapy was initiated. The mean onset was similar in the two groups [Table/Fig-3].

The healing duration was longer in the intervention group but was not statistically significant (p =0.167). [Table/Fig-3] shows a detailed

Grade	0	1	2	3	4
Clinical status	No oral mucositis	Erythema and soreness	Ulcers, able to eat solid foods	Ulcers, requires liquid diet (due to mucositis)	Ulcers, chewing not possible (due to mucositis)

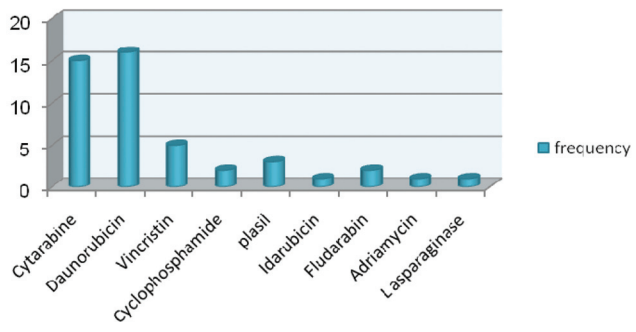
[Table/Fig-1]: WHO scale for assessing oral mucositis [31].



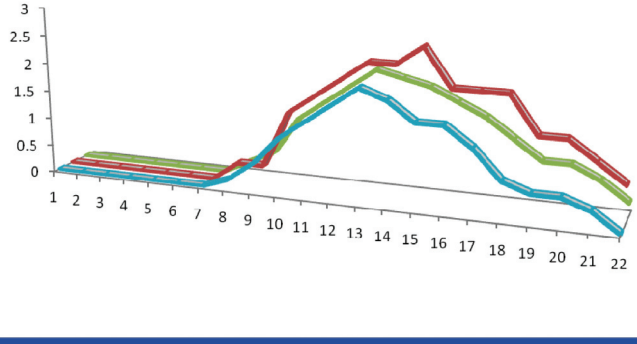
[Table/Fig-2]: Study flow diagram.

Variables	Age range	Mean age	Blood dyscrasia AML*,ALL**	Incidence of mucositis	Mean severity of mucositis in total study population	Mean disease-free time	Mean onset of mucositis (day after initiation of chemotherapy) in involved patients(n=9)	Mean duration of healing of mucositis(days)
Case	19–68	33±17	8,2	3	0.8±1.30	17.30±6	9.67	14±4.16
Control	15–65	33±16	7,3	6	1.3±1.16	13.4±6.57	9.33	10±2.26
P-value	0.946	0.946	0.615	0.189	0.379	0.218	0.756	0.167
Total	15–68	33±15.9	15,5	9	1.05±1.23	15.35±6.44	9.44±1.00	11.78±3.34

[Table/Fig-3]: Main study findings.



[Table/Fig-4]: Chemotherapy regimens in the study population.



[Table/Fig-5]: Mean severity of oral mucositis (vertical axis) in the intervention group (red line), the control group (blue line), and the total study population (green line) due to days after initiation of chemotherapy (horizontal axis).

description of the patients' data. Analysis showed a reduced risk of OM with 50% (CI=0.02–50.397) Relative Risk (RR) in the intervention group compared to the control group.

DISCUSSION

OM is a common and debilitating complication of cancer treatment with many clinical and economic outcomes; thus, many studies have been conducted. Perhaps the most aversive outcome of OM is the inability to intake food orally. Although many local and systemic modalities have been suggested for preventing and treating OM, little evidence is available to support a specific and effective treatment. Each treatment may lead to complications that must be considered. Some guidelines and oral care protocols has been suggested for managing oral mucositis that are not globally accepted [31-36].

In this randomized clinical trial, quercetin, an herbal flavonoid, was used to prevent and treat chemotherapy induced oral mucositis. This flavonoid is safe, absorbs adequately, and is not expensive. Many studies have shown anti-inflammatory properties of quercetin. Sotnikova R planned an in vivo study to reveal efficacy of two derivatives of quercetin (chloronaphthoquinone quercetin and monochloropivaloyl quercetin) in prevention of ulcerative colitis in rats. He concluded that chloronaphthoquinone quercetin can depress inflammatory damage to the colon although the exact mechanism remains unclear [36]. Effect of quercetin on oxaliplatin induced peripheral neuropathy was assessed by Azevedo MI et al., an animal study on mice showed that quercetin can inhibit thermal and mechanical nociceptive response in dorsal horn via decreased inducible nitric oxide synthase [37]. Another study on nano quercetin showed that downregulating MMP-9 and NOS-2 by this drug can prevent ethanol induced gastric inflammation in rats [38]. Several studies have shown that quercetin can protect gastric mucosa from ulceration [39-44]. This protective effect works due to antioxidative mechanisms such as inhibition of lipid peroxidation, decrease of reactive oxygen metabolites, inhibition of neutrophil infiltration, increase of superoxide dismutase activity, increased gastric mucus secretion, inhibition of free radical production by activated neutrophils via ICAM-1, and pro-inflammatory cytokine down regulation [40-44]. Evidence about anti-inflammatory effect of quercetin on oral ulcers is lacking. In a study by Hamdy AA showed that topical quercetin can improve recurrent aphthous stomatitis [23]. Effect of quercetin on prevention and treatment of chemotherapy induced OM was assessed in our study. Twenty-three patients were enrolled in this study. Three patients were excluded; thus, 20 patients finished the trial. Eight men and 12 women with a mean age of 33-year-old were randomly assigned to two study groups. The chemotherapy regimens were similar in both groups; therefore, OM was not related to the chemotherapy drugs. The incidence of mucositis was lower in the intervention group (3 of 10 vs 6 of 10). This difference was not statistically significant (p=0.189), but perhaps quercetin has some protective effect on OM.

Qutob AF et al., performed a systematic review to assess a preventive model for oral mucositis in children [45]. There was not enough evidence to support any modality (chlorhexidin mouthwash, laser therapy, glutamine, etc.,) for preventing OM. They concluded that oral sucralfate suspension, prostaglandin E2 tablets, and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) mouthwashes should not be considered in preventing OM due to the strength of evidence against their use. The authors showed that evidence is in favour of oral care protocols; thus, the only confirmed preventive means is oral health care. Another systematic review showed that oral cryotherapy can prevent OM in patients receiving bolus fluorouracil (5-FU) or high-dose melphalan [13]. In our study, the three patients in the intervention group with OM had more severe OM than those affected in the control group. They had a poor oral health status due to the severity of systemic disease. We did not compare oral health status in the groups because criteria of oral health were not used.

We used 250 mg quercetin BID. The maximum daily use for quercetin is 1500 mg, but due to special medical situation of the patient and the risk of unknown adverse drug effects and interactions, we used the minimal effective dose.

In our study, 20% of the intervention group had Grade 3 OM, but none of the control group had Grade 3 and 4 OM. Interventions

to reduce OM severity have shown that paliformin, triclosan, zinc sulfate, and chlorhexidin can be effective, but further research is necessary to obtain enough evidence. A systematic review showed that low-level laser therapy can be helpful in preventing OM in patients undergoing radiotherapy without concomitant chemotherapy for head and neck cancer, but was not feasible for other treatment settings. Palifermin and GM-CSF may be useful in preventing OM in patients receiving allograft stem cell transplantation. In a Cochrane systematic review, 10 interventions including aloevera, amifostine, cryotherapy, granulocyte-colony stimulating factor (G-CSF), intravenous glutamine, honey, keratinocyte growth factor, laser, Polymixin/Tobramycin/Amphotericin (PTA) antibiotic pastille/paste, and sucralfate had some benefit (albeit sometimes weak) for preventing or treating OM, although the researcher observed that the benefit may be specific for treatment of certain types of cancer and subgroup analysis must be performed in larger study populations [17].

Rodriguez-Caballero A et al., performed a critical review and concluded that it is necessary to combine interventions that act on the different phases of OM. We showed that quercetin can reduce the total relative risk of OM (30% vs 60%), but the risk of Grade 3 and 4 OM was high in the intervention group (20% vs 0%) [46].

Quercetin has a biphasic anti-inflammatory effect. At a lower dose, lymphocytes are irritated, but at higher doses, quercetin has an inhibitory effect on lymphocytes. Using higher doses might prevent or treat OM effectively; however, further study is needed to reveal the effect of administering quercetin in preventing and treating OM [20].

Quercetin is an herbal medication with little adverse reaction. If future research confirms using this drug in treating OM, it would be of great help. This study has several limitations, such as small sample size and the patients' poor oral health state. We suggest future studies use a larger sample and higher quercetin dose and control oral health status by using the oral health index in study groups.

CONCLUSION

Quercetin could prevent OM in intervention group but further research with larger sample size and more controlled clinical setting is recommended.

Conflict of interest disclosure

The authors declare no competing financial interests with any product mentioned in this manuscript.

ACKNOWLEDGEMENTS

Mashhad University of Medical Sciences supported this work. PK was a DDS (Doctor of Dental Surgery) candidate at Mashhad University, and this work is submitted in partial fulfilment of the requirements for the DDS thesis.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 06, 2016**
Date of Peer Review: **Oct 10, 2016**
Date of Acceptance: **Dec 04, 2016**
Date of Publishing: **Mar 01, 2017**