

Original Article

Comparison of therapeutic effects of statins and aloe vera mouthwash on chemotherapy induced oral mucositis

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Abstract: Background: Chemotherapy induced oral mucositis is a common problem among patients with cancer. Different therapeutic agents have been evaluated to prevent or treat the disease. Here we aimed to compare therapeutic effects of atorvastatin and aloe vera mouthwash on chemotherapy induced oral mucositis. Methods: 120 patients with large intestine and gastric cancer who were treated with 5-fluorouracil (FOLFOX4) for the first time were entered and randomized into 3 groups. Group 1 received tablets of atorvastatin 10 mg daily until 2 weeks after chemotherapy sessions plus placebo mouthwash. Group 2 received aloe vera mouthwash plus placebo tablets and group 3 received placebo mouthwash and placebo tablets until 2 weeks after chemotherapy sessions. Severity of mucositis was assessed using world health organization (WHO) indexes. Based on this method, mucositis is divided into 4 grades. This study was approved by Iranian Registry of Clinical Trials (IRCT) with the code of: IRCT20201203049585N1 (<https://fa.irct.ir/trial/54037>). Results: Analysis of the incidence of mucositis among patients showed that in placebo group, 50% of patients experienced grade 2 to 4 mucositis. In group 1, 9 patients (22.5%) had grade 2 mucositis and 6 patients (15%) had grade 3 mucositis and 4 patients (10%) had grade 4 mucositis. In group 2, only 1 patient (2.5%) was diagnosed with grade 2 mucositis. These data showed no significant differences between group 1 and group 3 ($P=0.674$), but the therapeutic results of group 2 were significantly better than those of group 3 ($P=0.042$) and group 1 ($P=0.036$). Conclusion: We showed that treatments with aloe vera mouthwash could be an effective choice in prevention of mucositis for patients undergoing chemotherapy. There are also much to discover about effects of aloe vera mouthwash on this disease.

Keywords: Mucositis, atorvastatin, aloe vera, cancer, chemotherapy

Introduction

In the last decades, prevalence of cancer has increased among different developing and developed countries due to both environmental and genetic factors [1, 2]. Chemotherapy, radiotherapy, immunotherapy and surgeries are some of the most common strategies [3-5]. In cancer patients, increased vulnerability of patients to different local or systemic infections are observed [6, 7]. Oral infections are prevalent among these patients that have also the ability to become disseminated or even

cause septicemia [8]. Studies showed that early diagnosis and managements of such infections are pivotal in cancer patients [9, 10].

Stomatitis or oral mucositis is known as a general and painful complication of chemotherapy [11]. Researches have been conducted on the pathophysiology of mucositis in cancer patients. Scientists believe that chemotherapy drugs which limit or inhibit cell growth and meiosis in cancer tissue will also influence on tissues with high cell growth rates such as gastrointestinal or skin tissue [12]. Clinically, effects of chemo-

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therapy drugs appear within the first or second weeks after beginning of chemotherapy. Epidemiologic data indicate that mucositis could be observed in 40% of patients receiving primary chemotherapy and 10% of patients who receive adjuvant chemotherapy [13]. Different causes of mucositis have been indicated among variable studies. It has been proven that type β interleukin 1 (IL-1), free radicals, prostaglandins and type α tumor necrosis factor (TNF- α) play important roles in development of mucositis [14, 15]. Clinically, mucositis begins with mild erythema followed by edema, painful ulcer, hemorrhagic ulcer and secondary infections. Opportunistic infections including candidiasis could also be detected in these patients due to malfunctions in immune system [16]. Another complication of mucositis is malnutrition in cancer patients [17].

Different therapeutic agents have been utilized in cancer patients who have mucositis. Statins are HMG-CoA reductase inhibitors which are widely being administered due to their effectiveness in modulating lipid profiles in patients and also preventing cardiovascular diseases [18]. Studies have indicated that statins might also have anti-inflammatory properties and inhibit the mevalonate synthesis pathway [19]. By this way, they could have positive effects on reducing inflammation in different diseases and help wound healing process [20]. Effects of statins on mucositis have been assessed mostly among animal models [21].

Aloe vera mouthwash is a therapeutic agent which has been used in cancer patients. Promising results have been reported by scientists about preventive effects of aloe vera mouthwash against mucositis [22]. In a study by Sahebamee and others, effects of aloe vera and benzidamine mouthwashes were evaluated and compared in cancer patients. They concluded that both aloe vera and benzidamine mouthwashes could prevent oral mucositis but aloe vera has no serious complication compared with benzidamine [23].

So far, some variable therapeutic agents have been used to reduce chemotherapy induced mucositis in patients and variable results have been reported. Here in this study, we aimed to investigate and compare the effects of atorvastatin with aloe vera mouthwash in prevention

and treatments of mucositis in patients under chemotherapy.

Methods and material

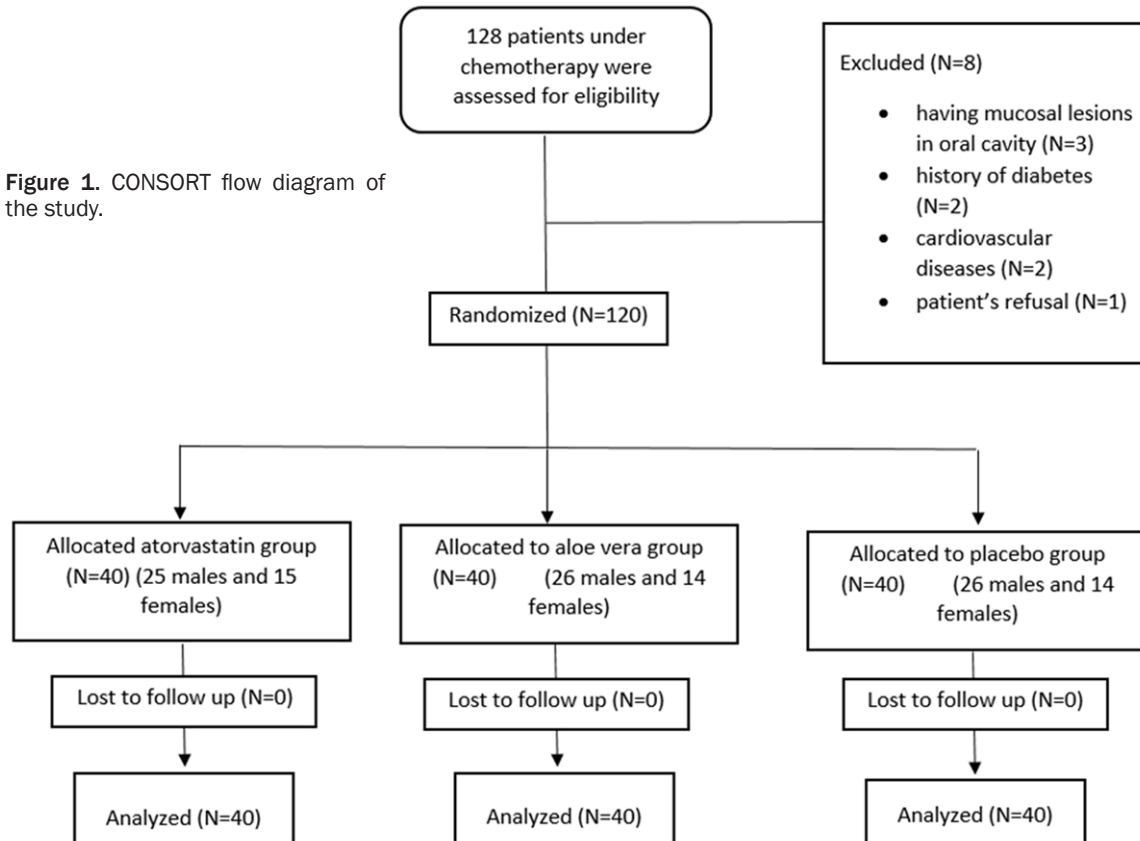
This is a double-blinded randomized clinical trial which was performed on patients with large intestine and gastric cancer who were treated with 5-fluorouracil (FOLFOX4) for the first time. The present study was performed in 2019 in Imam Hossein hospital and Saadat clinic in Tehran, Iran. This study was approved ethically by the ethical committee of Tehran University of Medical Sciences (Ethics code: TUMS.MED.REC.91.130.926.S).

Our inclusion criteria were: documented large intestine or gastric cancer verified by oncologists, age between 20-65 years, and first-time treatment with 5-fluorouracil (FOLFOX4). The exclusion criteria were: neutropenia, history of diabetes, having mucosal lesion in oral cavity before treatments, history of radiotherapy, being under treatments with hormonal drugs (with estrogen or anti-estrogen effects), history of cardiovascular diseases, and poor oral hygiene (presence of gingivitis or dental caries on more than three teeth) as diagnosed by a dental expert.

A total number of 120 patients were recruited in our study. The written informed consent was signed by all patients. Patients were randomly divided into 3 groups each containing 40 patients: group 1 received tablets of atorvastatin 10 mg daily until 2 weeks after chemotherapy sessions plus placebo mouthwash containing drinking water 94.5%, pear concentrate 5%, lemon flavoring 0.4% and citric acid 0.1% with same smell and taste of aloe vera mouthwash. Group 2 received aloe vera mouthwash containing 94.5% aloe vera extract (reconstituted from concentrate), pear concentrate 5%, lemon flavoring 0.4% and citric acid 0.1% plus placebo tablets containing glucose with the same shape and tastes of atorvastatin tablets. Group 3 received placebo mouthwash and placebo tablets until 2 weeks after chemotherapy sessions. Patients were visited and examined every 2 days by our research team for any clinical presentations of mucositis. Both patients and researchers were unaware of the groups of patients and type of the administered drugs.

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Figure 1. CONSORT flow diagram of the study.



Severity of mucositis was assessed using world health organization (WHO) indexes. Based on this method, mucositis is divided into 4 grades. Grade 1: no visible ulcer and only erythema. Grade 2: presence of small ulcer and erythema despite the ability of eating in patient. Grade 3: diffuse ulcers more than 25% of the oral cavity surface are observed and the patient has only the ability of drinking liquids. Grade 4: hemorrhagic ulcers are observed and the patient has no ability to eat or drink. Patients were also observed for any possible drug complications or electrolytes disruptions and if such side effects were reported, the patient was excluded. Data were collected and analyzed using SPSS software version 24. We used Mann-Whitney tests, independent T test and chi square tests in order to analyze the data.

Results

Here in the present study, 128 patients were entered. 8 patients were excluded before the study initiated. 3 patients due to having mucosal lesions in oral cavity, 2 patients due to his-

tory of diabetes, 2 patients due to cardiovascular diseases and 1 patient due to refusal. During the study, no patients were excluded and no complication or side effects were reported. The CONSORT diagram of the current study is indicated in **Figure 1**. Primary analysis of demographic data showed that 77 patients (64.1%) were male and 43 patients (35.9%) were female. Our initial analysis showed that 94 patients (78.3%) had large intestine cancer while 26 patients (21.7%) had gastric cancer. None of the patients had metastasis. Mean age of patients were 55.20 ± 7.74 years and the mean duration between diagnosis of cancer and chemotherapy was 4.97 ± 2.88 months. Comparison of the mean age and sex and duration between diagnosis of cancer and chemotherapy indicated no significant differences between 3 groups of patients ($P > 0.05$). These data are summarized in **Table 1**.

Further analysis of age groups (less than 50 years and more than 50 years) indicated that 78% of all patients were more than 50 years old. We also showed that in more than 34% of patients, duration time between diagnosis and

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Table 1. Baseline patient characteristics

Variable	Males (n (%))	Females (n (%))	Mean age (mean ± SD) (years)	Duration between diagnosis and treatments (mean ± SD) (months)	P-value
Group 1	25 (62.5%)	15 (37.5%)	54.23±7.64	4.99±2.56	>0.05
Group 2	26 (65.0%)	14 (35.0%)	56.31±7.43	4.90±3.44	
Group 3	26 (65.0%)	14 (35.0%)	55.06±8.14	5.02±2.63	

Table 2. Comparison of mucositis between atorvastatin and placebo groups

Variable	Grade 1 mucositis (n (%))	Grade 2 mucositis (n (%))	Grade 3 mucositis (n (%))	Grade 4 mucositis (n (%))	Total (n (%))	P-value
Group 1	21 (52.5%)	9 (22.5%)	6 (15%)	4 (10%)	40 (100%)	0.674
Group 3	20 (50%)	10 (25%)	7 (17.5%)	3 (7.5%)	40 (100%)	

Table 3. Comparison of mucositis between aloe vera and placebo groups

Variable	Grade 1 mucositis (n (%))	Grade 2 mucositis (n (%))	Grade 3 mucositis (n (%))	Grade 4 mucositis (n (%))	Total (n (%))	P-value
Group 2	39 (97.5%)	1 (2.5%)	0	0	40 (100%)	0.042
Group 3	20 (50%)	10 (25%)	7 (17.5%)	3 (7.5%)	40 (100%)	

Table 4. Comparison of mucositis between atorvastatin and aloe vera groups

Variable	Grade 1 mucositis (n (%))	Grade 2 mucositis (n (%))	Grade 3 mucositis (n (%))	Grade 4 mucositis (n (%))	Total (n (%))	P-value
Group 1	21 (52.5%)	9 (22.5%)	6 (15%)	4 (10%)	40 (100%)	0.036
Group 2	39 (97.5%)	1 (2.5%)	0	0	40 (100%)	

treatments was more than 6 months. Evaluating types of cancer, we showed that 47% of patients had gastric cancer.

Analysis of the incidence of mucositis among patients showed that in placebo group, 50% of patients experienced grade 2 to 4 mucositis. In group 1, 9 patients (22.5%) had grade 2 mucositis and 6 patients (15%) had grade 3 mucositis and 4 patients (10%) had grade 4 mucositis. In group 2, only 1 patient (2.5%) was diagnosed with grade 2 mucositis. Data regarding to prevalence of mucositis in different groups are summarized in **Tables 2-4**. These data showed no significant differences between group 1 and group 3 (P=0.674), but the therapeutic results of group 2 were significantly better than those of group 3 (P=0.042) and group 1 (P=0.036).

Discussion

Here in the present study, we evaluated the therapeutic effects of atorvastatin and aloe vera mouthwash on chemotherapy induced

mucositis and compared them with controls. Our results showed that the grade 3 and 4 mucositis were more prevalent among patients treated with placebo compared to atorvastatin. None of the patients that received aloe vera mouthwash had grade 3 and 4 mucositis. Comparison of atorvastatin and aloe vera mouthwash group, our results indicated that 97.5% of patients that received aloe vera mouthwash had grade 1 and 2.5% had grade 2 mucositis but 52.5% of atorvastatin group had grade 1 and 22.5% had grade 2 and 15% had grade 3 mucositis that indicated a better therapeutic condition for aloe vera mouthwash. Different lines of evidence have evaluated therapeutic effects of different agents on chemotherapy induced mucositis and reported variable results [24-26].

Most of the previous studies about aloe vera mouthwashes had been performed on radiation induced mucositis, reporting beneficial effects of this agent. Ahmadi has assessed influences of aloe vera mouthwash on oral mucositis induced by radiation in patients with

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head and neck cancer. This paper reported beneficial effects for aloe vera mouthwash in prevention of mucositis and reduction of inflammation in patients [27]. It has also been reported that aloe vera is able to prevent candidiasis in patients. Freitas Cuba and others also reported that aloe vera and vitamin E are able to reduce inflammation in oral mucus and induce healing process in animal models of radiation induced mucositis [28]. These results are in line with what we reported. An important point of our study is that we compared therapeutic effects of aloe vera mouthwash and atorvastatin tablets and showed that both drugs exhibit protective effects compared to controls. Furthermore, Kumar and Tiku have evaluated immunomodulatory potentials of acemannan which is a polysaccharide derived from aloe vera. They reported that aloe vera can act by induction of hematopoiesis and upregulation of cytokines like TNF- α and IL-1 in radiation induced animals. These mechanisms and especially immunomodulation could contribute to reduced inflammation and as a result, reduced mortality rates [29].

Statins have exhibited valuable results in different clinical trials on both humans and animals. In a study performed by Konings and colleagues in 2010, effects of pravastatin in ameliorating chemotherapy induced mucositis were assessed among 30 patients with gastric cancer. They reported that addition of pravastatin to chemotherapy regime of epirubicin, cisplatin and capecitabine was not associated with significant changes in patient's conditions [30]. These results are not in line with the results of our study. Here we showed that atorvastatin was significantly effective and beneficial in prevention of mucositis in patients under chemotherapy compared to controls. These variations could be due to differences in the methods and study population of our study and the study of Konings and colleagues. Here we performed this study on 120 patients being treated with 5-fluorouracil (FOLFOX4) and we administered atorvastatin tablets while they evaluated 30 patients treated with epirubicin, cisplatin and capecitabine and they administered pravastatin. In another study by Medeiros and others in 2011, effects of atorvastatin on chemotherapy induced mucositis in hamsters and declared that atorvastatin at doses of 1 and 5 mg/kg reduced mucosal damage and

inflammation [31] which is completely in line with our results. Simvastatin was also assessed in prevention of chemotherapy induced mucositis in rats. Azevedo and others reported beneficial effects for simvastatin in animal models of the disease [32].

These results put emphasis on beneficial effects of aloe vera mouthwash on mucositis among cancer patients. Although some animal studies indicated effectiveness of statins on chemotherapy induced mucositis, but there are still lack of evidence about human trials. There have also been clinical trials on humans about the protective effects of aloe vera. As Sahebamee and colleagues have indicated, both aloe vera and benzydamine mouthwashes were efficient in reducing the severity of oral mucositis in 26 patients with head and neck cancer [33]. These effects have also been reported by Mangaiyarkarasi and colleagues [34] but so far, no previous study has evaluated and compared beneficial effects of aloe vera mouthwash and atorvastatin among chemotherapy induced mucositis. For the first time, we showed that both aloe vera mouthwash and atorvastatin have positive effects on chemotherapy induced mucositis. We should also note that commercially available aloe vera concentrates may vary in terms of chemical composition, the findings of this study may not translate to another institution with a different supplier.

Conclusion

Taken together, we showed that treatments with aloe vera mouthwash could be an effective choice in prevention of mucositis for patients undergoing chemotherapy. This issue has been evaluated and declared by previous studies. There is also much to discover about effects of aloe vera mouthwash on this disease. We suggest that physicians should add aloe vera mouthwash to treatment regimes in cancer patients undergoing chemotherapy.

Disclosure of conflict of interest

None.

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