Evaluation the effect of Gum Arabic as prophylactic agent against chemotherapy-induced oral mucositis in cancer patients: A clinical trial

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Abstract

Several of oral problems such as mucositis, dry mouth and dysphagia associated with cancer therapy have significant impact on the physical status, social, and psychological behavior of cancer patients to varying degrees. The purpose of this research was to investigate the effect of Gum Arabic to prevent chemotherapy-induced oral mucositis in cancer patients. A clinical trial was conducted for a total of 374 cancer patients (14-80 years of age). Patients were categorized into two groups; 190 in the study group and 184 in the control group. The study group, who received chemotherapy were given a dose of 30 grams per day Gum Arabic orally for six weeks, while the control group received only chemotherapy. Essential data concerning the patients were recorded, and the assessment of oral mucositis was carried out weekly for six weeks. This study showed a significant (P = 0.001) reduction in the incidence of chemotherapy-induced oral mucositis in the fourth week and in the sixth week (P = 0.002). This study concluded that the regular administration of Gum Arabic has beneficial effects for cancer patients against oral mucositis induced by chemotherapy. This work registered at ClinicalTrials.gov by the following Identifier number: NCT03348241.

Introduction

One of the commonest oral complications of cancer therapy is oral mucositis. It is a term that describes inflammation of oral mucosa resulting from chemotherapeutic agents or ionizing radiation (observed in the majority of patients receiving radiotherapy for head and neck cancer) [1-3]. It affects approximately 20% to 40% of patients receiving conventional chemotherapy regimens for solid tumors, depending on the dose and cytotoxicity of the drug [4]. Clinical outcomes of oral mucositis in cancer patients, which may result in reduction or delay of the dose, can be summarized in follow: weight loss (due to decreased oral intake) [5], occurrence the pain representing the specific symptom for most patients with mucositis [6]; elevation of the risk of systemic infection; decrease in overall survival among patients with severe mucositis [7].

In patients receiving chemotherapy, a reduction in the next dose of chemotherapy was twice as common after cycles with mucositis than after cycles without mucositis [8]. The treatment of oral mucositis is empiric, since there is no evidence-based standard treatment protocol. Discovery of the agents which can be used to prevent or treat chemotherapy-induced oral mucositis is a primary concern for clinicians and researchers. An oral care solutions or products for mucositis in cancer patients needed to reduce the oral flora, should have a pleasant taste, reduce oral pH, assist in the re-epithelialization of the oral mucosa and be non-irritating to the oral tissue and non-toxic. Several recent systematic reviews on this topic have been published, however, there is insufficient evidence to make clinical recommendations for practice. The best options for managing chemo-radiotherapy-induced mucositis are good oral hygiene and regular assessment of the patient [9].

The synthesis of pharmacological drugs is costly and associated with much side effects resulting in patient non-compliance. So, there is a need to find alternative therapies especially from natural sources

as these are cost effective and have no or minimal side effects. In this regard, Gum Arabic (GA) is very convenient since this polymer is readily available in nature and does not require any further complex methods of purification. Also it is a safe material for biological applications.

Gum acacia, also known as Gum Arabic is exuded from acacia trees; mainly from *Acacia Senegal* (gum hashab or Kordofan gum) and *Acacia Seyal* (Gum Talha). According to several previous studies; no significant adverse or toxic effects have been associated with the use of GA [10,11]. Gum Arabic is a little acidic compound, comprised of polysaccharides, glycoproteins and some of major cationic elements that including calcium, magnesium, sodium, potassium, iron and copper [12,13].

There were several studies conducted on the Gum Arabic which indicated an important medical uses, such as cardio-protective against toxicity induced by doxorubicin [14], improvement in both renal and cardiovascular outcome in normal individuals [15], antihypertensive effects [16,17], improvement and treatment of chronic renal failure [18-20], cytoprotective against drugs/agents-induced renal toxicity [21-25], prophylactic or treatment of obesity [26-29] and improving lipid profile [30-34], protection against hepatic oxidative stress [35,36] and drug-induced hepatotoxicity [37], antioxidant property [18,38-41], anti-inflammatory activity [19,42,43] and immunoregulatory effect [44].

The objective of this study is to evaluate the effectiveness of Gum Arabic in prevention of chemotherapy-induced oral mucositis in cancer patients. Our prediction is that, the patients of treated group (receiving Gum Arabic with chemotherapy) may show chemotherapy-induced oral mucositis less than that in control group patients (chemotherapy alone).

Results

As shown in Table 1 the minimum and the maximum of patients' ages were 14 and 80 years respectively; (mean age value was 47.2 years). Most patients in this study were Sudanese; 30% of them were males and 70% were females. The heights of the patients ranged from 120 to 192 cm with a mean of 163.7 cm. The weights of the patients were in the range 30-120 Kg and the mean was 61.4 Kg. The body surface area ranged from 1.1 to 2 m^2.

Among the major cancer types, the breast cancer comprised the highest percentage of the female patients (36%), followed by the gastro-intestinal tract cancer (19%) and gynecological cancer (17%). The lowest percentage of cases was found in patients infected by skin cancer which was (1%) Fig. (1).

Results obtained during six weeks of follow-up are summarized in Tables 2. The chemotherapy-induced oral mucositis exhibited by the patients in the GA-treated group was generally less than that in the control group. Except for the fourth and the sixth weeks during which analysis of the data collected on the incidence of oral mucosiris revealed significant differences (P = 0.001 and = 0.002 respectively) between the two groups, results obtained during the remaining four weeks were statistically non-significant (Table 3)

Although the percentages of patients in the GA-treated group showing oral mucositis increased from 11.7% in the first week to 20.5% in the second week which consequently increased the percentages of patients without oral mucositis, it dropped to 8.6% in the third week. Results obtained with the patients in the control group showed a similar trend. Percentage of GA- treated patients with oral mucositis dropped even more in the fourth week as shown in Table 2, only 5.3% had oral mucositis. On the contrary patients in the control group showed more percentage incidence of oral mucositis (16%) in the fourth week as compared to the third week (14%). The difference between the two groups as mentioned above was significant. However, in the fifth week the percentage of patients with oral mucositis increased to 12% in the GA-treated patients and to 20% in the control but dropped again in the sixth week to significantly lower values of 4.8% for patients treated with GA and 15.1% for patients in the control group. Figure 3 summarized percentages of oral mucositis incidence during the six weeks in the two groups.

As shown in Supplementary Table 1, Chi-Square tests of the data on cancer type in relation to presence or absence of oral mucositis revealed significant (P = 0.05) difference among patients in the control group during the first week. However, no similar result was obtained in either group of patients in the remaining weeks. Results of Chi-Square test (Supplementary Table 2) also showed significant relations between type of chemotherapy and presence or absence of oral mucositis in the sixth week in the GA-treated group, but no significant relationship was found in the other weeks either in the treated or in the control group.

Side effects caused by GA administration were experienced only in the first week. They included unfavorable viscous sensation in the mouth, early morning nausea and bloating abdomen.

Discussion

Extensive review of the literature on the different agents and methods used for the management of oral mucositis showed no conclusive results as concerns the efficacy of any of them in preventing incidence of this extremely dangerous side effect of cancer chemo/radiotherapy. However, the use of GA in case of some other diseases provided sufficient evidence to support its beneficial impacts for preventing oral mucositis since it is known to have powerful antioxidant, antimicrobial and anti-inflammatory effects [45-48]. So far no reports on the possible use of GA administration for preventing oral mucositis induced by chemo- or radiotherapy. Therefore, the present study is the first to assess the effects of orally administered GA on oral mucositis.

In this study, oral administration by cancer patients of 30 g of GA (Acacia Senegal spp.) as aqueous solution after commencement of chemotherapy seemed to cause significant reduction in incidence of oral mucositis after three weeks by which time mucositis might have reached the ulceration phase according to the pathobiology model of mucositis introduced by Sonis in 2004. Sonis (2009) found that bacterial colonization peaked synchronously with the mucositis score at three weeks. The bacteria on the ulcer surface are active contributors to the mucositis process. Recent studies have elucidated a shift to a more complex oral bacterial profile in patients undergoing cancer chemotherapy [49] which raised the

question whether these shifts may trigger the development of local or systemic infections in the long term. Some of the proinflammatory cytokines such as interleukins (IL b) and (IL 6) exert cellular damage and induce apoptosis during the phase of primary damage response according to the putative 5-step pathogenesis of chemotherapy and radiation-induced mucositis [50].

Results clearly indicated that the greatest percentages of patients showing mucositis either with or without GA treatment were in the second and the fifth weeks in respectively the first and the second cycles of chemotherapy. It is obvious that the increase in incidence in each cycle was due to the ulceration phase of mucositis which commenced a week after chemotherapy in the two cycles. Reductions in mucositis incidence were observed during the following two weeks with slight increase (from 14% to 16%) shown by the control group in the fourth week. However, the difference in incidence between the two groups at this week was statistically significant. At the sixth week mucositis incidence in the GA-treated group was significantly lower than that of the control. As a plausible explanation, the drop in incidence in the two cycles of chemotherapy might correspond to the healing phase which apparently accompanied with a significant reduction in incidence as compared with the control in the second cycle. This result gives an evidence for the effectiveness of GA as a prophylactic agent for preventing oral mucositis. Better understanding of the effects of cytotoxic therapy in causing oral mucosal changes is of utmost importance. It is likely that the effect of chemotherapeutic regimen on development of mucositis decreased appreciably at the end of each cycle of chemotherapy which seemingly approached or coincided with the healing phase.

The oral mucositis incidence percentage in this research is consistent with a study by Elting *et al.* [8] which indicated that the occurrence of oral mucositis was 22% of the total number of patients. It has been reported that prevalence and incidence of oral mucositis vary considerably due to the variation among tumor type locations, different treatment regimens, and a heterogeneity of standardized scoring criteria [51]. Assessment of the incidence of oral mucositis in the present study was carried out based on the description of WHO scores. The number of cancer locations recorded was 65 types in 392 of the participants, and they were treated through 64 chemotherapy regimens (Supplementary Tables 3 and 4 respectively). Also, the study revealed that at least eighteen regimens are considered the most chemotherapy regimen that cause oral mucositis between all cancer patients (Supplementary Tables 5).

Results indicated that regular intake of 30 g/day GA by the patients resulted in highly significant (P=0.001 and 0.002) reductions in the incidence of oral mucositis in the fourth and sixth weeks respectively. As a reasonable explanation for this result, the observed drop in the incidence of the oral mucositis could be due to the antioxidant activity of Gum Arabic [22,35,36]. It may also be attributed to its free radical scavenging property which reduces the oxidants parameters (Malondialdehyde and nitric oxide) [18,47] generated by chemotherapy and cause damage to the connective tissues, DNA, and lipids; and consequently lead to the development of mucositis [52,53]. Moreover, increases in the levels of pro-inflammatory cytokines tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) are associated with the development of mucositis [50]. Therefore, Gum Arabic may act as anti-inflammatory

for the protection against cellular toxicity [14,20,21,54]. These findings support the idea that Gum Arabic act as anti-inflammatory to prevent or reduce the incidence of oral mucositis.

Because the weekly follows up of oral mucositis assessment was based on the patient's description through answering specific questions, it was found difficult to classify oral mucositis according to the WHO grades, despite the fact that even mild mucositis may represent a burden to the patients.

The delay of onset of GA action may be attributed to that the use of Gum Arabic was with the outset of chemotherapy and this may not be enough to achieve its effects against oral mucositis. However, the possibility of Gum Arabic administration pre-chemotherapy will be considered in later studies.

Dose-dependent effect of GA on oral mucositis in cancer patients, may open a new area for future studies as to determine the most effective dose and the time of administration for curing the oral mucositis. Although it was proposed to give pectin as placebo for the control group, but it would, perhaps be difficult to make sure that the patients would be willing to use an unknown substance while they were at home. There was also difficulty in make this study blind, that because the Gum Arabic is popularly known in Sudanese society and this what made the study open label.

One of the limitations in this study was that Gum Arabic was not given to cancer patients who were treated with high doses of chemotherapy, where the rate of oral mucositis incidence is expected to be higher compared to traditional doses of chemotherapy. Another limitation was the omission of placebo in case of the control group. It was excluded because of the unwillingness of the cancer patients to use anything other than their medicines, particularly when the substance is unknown.

This study provided more evidence that oral administration of GA (30g / day) as an aqueous solution for a period of six weeks had potent anti-oxidative and anti-microbial effects on oral mucositis induced by chemotherapy as demonstrated by its ability to significantly reduce the percent incidence of oral mucositis with every cycle of chemotherapy and also to shorten the duration of the ulceration phase. It provided further evidence for the beneficial use of GA which can be utilized in other clinical conditions and diseases caused by tissue injury.

Methods

Study design

It was an interventional clinical study using an open-label clinical trial. Patients were categorized into study and control groups.

Study population

After an official approval from Khartoum Oncology Hospital and written informed consent from the patients (signed by the participant) in outpatient chemotherapy wards, 374 patients were recruited for this study (shown in Fig. 1). Most the participants in this study were Sudanese, 30% males and 70% females

(ages ranged between 14 and 80 years). Only two participants under 16 years of age who involved in this study (as shown in Supplementary Table 6), where a written consent was obtained from their parents. Patients enrolled in this study were free from any comorbid disease other than the cancer.

Inclusion criteria

Patients who attended the studied hospital, then diagnosed with cancer, and received chemotherapy.

Exclusion criteria

Patients received recent chemotherapy or radiotherapy, had oral mucositis or periodontitis, or had evidence of any systemic diseases were excluded in this study.

Study area

This study was conducted in outpatients' chemotherapy sections at Khartoum Oncology Hospital, Sudan.

Materials

Patients in the study group received a dose of 30 grams GA per day as oral solution for six weeks along with the chemotherapy prescribed, while those in the control group received only chemotherapy regimen. Most of chemotherapy regimens were taken every 3 weeks for periods ranged from 4 to 8 cycles according to type of cancer, severity grade and type of chemotherapy (Supplementary Table 5).

Three hundred kilograms Gum Arabic were crushed by electrical grinder in 1 mm particle size, then packed up in plastic bags. Plastic sachets with the capacity of thirty grams were used. Individual daily dose was weighed manually using digital balance. Impulse sealer was used to seal sachet after filling with Gum Arabic. A suitable label containing information concerning the content, quantity, instructions for preparation of solution, instructions for use, and date of filling was designed and glued on each sachet. Plastic cups (250 milliliter capacity) were used to measure the water quantity required to prepare the solution of Gum Arabic.

Gum Arabic Preparation and Administration

The daily dose of GA was 30 g of 100% natural gum provided in a crushed form (1 mm in size). The dose was determined based on previous studies [97, 112, 142, 159, 160]. The required amount of GA was kept in a sachet, to be dissolved once in 250 ml bottled water to form a solution, and then consumed in two equal divided doses to be taken morning and evening. The total quantity of Gum Arabic sachets for each patient was prepared and consumed during a period not more than eight weeks to ensure the quality of product and avoiding its exposure to humidity. Patients in GA-group were followed up weekly to assure their adherence to Gum Arabic administration.

The total number of sachets per patient was 42; each patient was given 21 sachets of GA at the first day of chemotherapy to be used during the next three weeks of the treatment period, then the remaining

sachets (21) was provided for the next three weeks.

Study period

The patients of treated group were enrolled and followed up for five months (from October 2015 to February 2016). The recruitment of new cases was suspended for a period of three weeks so as to reduce the probability that some information may be leaked from patients in the GA-treated group to the other group concerning the effects of GA in curing the oral mucositis. Then the collection and follow up of control group patients started and continued for six months (from March to August 2016). Since the sample size proposed and follow up planned were completed, no further recruitment or follow up was made.

Ethical considerations

According to the Omdurman Islamic University regulations and based on the clinical trials guidelines, the proposed protocol for this study was approved in the meeting of the Research Council of the College of Pharmacy No. (18) dated 5/4/2105. An ethical approval was obtained from Directorate of Research and Training in the Ministry of Health Khartoum State. A permission also obtained from Khartoum Oncology Hospital authority. In addition, a written consent was obtained from the participants prior to their enrollment in the study. All procedures of this clinical trial were performed in accordance with relevant guidelines and regulations.

Data collection

Data collected were recorded on sheets prepared specially for this purpose (Supplementary Table 7). Each sheet was composed of two sections: the first contained a table of WHO for Oral Mucositis Assessment, and it was filled during a period of six weeks of patient follow- up, through weekly telephone calls based on ready-scheduled appointments for Gum Arabic and control groups (Supplementary Tables 8 and 9 respectively). The second contains basic information and characteristics of the patient, and this was filled on the first day of the first cycle of chemotherapy. In addition, meetings were also arranged with the patients in chemotherapy rooms when they returned to the next cycle of chemotherapy either weekly, bi-weekly or every three weeks according to their treatment regimen.

Occurrence of Oral Mucositis

Presence or absence of oral mucositis in cancer patients who were to receive chemotherapy was made in accordance with the patient's description after starting of the treatment. They were newly diagnosed cases and, therefore, free from oral mucositis. However, measuring this outcome was also consistent with the main purpose of the present study.

During contacts or encounters, specific questions regarding oral mucositis were asked and they were answered by the participants. The questions were as follow:

a. Does oral mucositis is present or occurred during the week?
b. If the answer was yes; the patient would be asked about the occurrence of soreness, erythema, or ulcers in his/her mouth?
c. The participant also was asked about the day when oral mucositis started and if it present or ended?
d. If the participant belongs to the study group; then would be asked about whether his/her use of Gum Arabic solution was regularly or not?

Compliance was monitored via weekly follow-up and contacts with the patients by telephone calls. All data were recorded and stored carefully to ensure patient confidentiality.

Sample size and recruitment

Patients who met the study criteria and agreed to participate in this study were randomly selected from Outpatient Chemotherapy Sections of males and females' wards. The selection process was done by the case-finding method based on the daily new admission for cancer patients who decided to receive chemotherapy. According to the Clinical Trial Phases [57]; 374 patients were selected to achieve the required number of subjects for the phase II clinical trial.

Out of the total number of patients eleven died during the period of six weeks of follow-up (3 from the GA-treated group and 8 from the control group); nine patients from the GA-treated group withdrawn and thirteen other patients (two from the GA-treated group and eleven from the control) excluded because all were unreachable after recruitment (Figure 1).

The selection of patients who met the study criteria and who served as GA-treated group was during the period from October 2015 to February 2016. Then the recruitment of new subjects as control group was started after three weeks to reduce the probability that some information may be leaked from patients in the GA-treated group to the other group concerning the effects of GA in curing the oral mucositis. Collection of data and follow- up of control group patients started in March (2016) and continued for six months (August 2016). After that recruitment of new patients and follow-up were stopped; since the sample size proposed and follow- up planned were completed. The selection of sample size and recruitments the patients were done by the investigator.

Statistical analysis

The collected data were arranged, coded, tabulated and then analyzed using Statistical Package for Social Science (IBM SPSS Statistics version 25). Student t test was used to assess the statistical significance of the difference between means of the two groups. P. values equal or less than 0.05 were considered significant. Data of 332 patients who completed this study were documented and subjected to further analysis.

Declarations

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Registration

This study registered on 17th November 2017 at ClinicalTrials.gov by Identifier number**:** NCT03348241

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Author Contributions

A.Y.A. designed the research study, implemented the steps of research, collected and analyzed the data and prepared the paper to publication. A.H.M. supervisor on the theoretical part of this study. A.E.E. supervisor on the practical part of this work in the hospital. W.S.S. contributed by advice, constructive criticism and encouragement throughout the course of the study. The authors read and approved the final manuscript."

Additional information

Competing interests

The authors declare that they have no any competing interests (financial and non-financial interests).

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Tables

Table 1 Demographics and baseline characteristics

Characteristics	Minimum		Maximum		Mean		Std. deviation	
	Gum Arabic	Control	Gum Arabic	Control	Gum Arabic	Control	Gum Arabic	Control
Age (year)	16	14	80	80	46.5	47.9	13.5	13.4
Gender					30.6% Male 69.4% Female			
Height (cm)	120	128	190	192	162.9	164.5	9.5	8.5
Weight (Kg)	30	31	120	120	62.4	60.5	16.7	15
Body surface area (m^2)	1.1	1.1	2	2	1.6	1.6	0.2	0.2

Table 2 Numbers and percentages of patients with and without oral mucositis through six weeks of study.

Week	Group	Patients with oral mucositis		Patients without oral mucositis		Total No. of patients
		Frequency	Percent	Frequency	Percent	
First	Gum Arabic	18	11.7%	136	88.3%	154
	Control	22	12.6%	153	87.4%	175
Second	Gum Arabic	35	20.5%	136	79.5%	171
	Control	39	22.7%	133	77.3%	172
Third	Gum Arabic	15	8.6%	159	91.4%	174
	Control	25	14%	153	86%	178
Fourth	Gum Arabic	9	5.3%	160	94.7%	169
	Control	27	16%	141	84%	168
Fifth	Gum Arabic	20	12%	147	88%	167
	Control	33	20%	132	80%	165
Sixth	Gum Arabic	8	4.8%	160	95.2%	168
	Control	23	15.1%	128	84.9%	151

Table 3 Results of the t-test for comparing the mean differences in the mucositis incidence between Gum Arabic treated group and control group.

Week	Group type	Number of patients	Mean	SD	Sig. (2-tailed)
First	Gum Arabic	154	1.88	0.32	0.793
	Control	175	1.87	0.33	
Second	Gum Arabic	171	1.80	0.41	0.621
	Control	172	1.77	0.42	
Third	Gum Arabic	174	1.91	0.28	0.109
	Control	178	1.86	0.35	
Fourth	Gum Arabic	169	1.95	0.23	0.001
	Control	168	1.84	0.37	
Fifth	Gum Arabic	167	1.88	0.33	0.057
	Control	165	1.80	0.40	
Sixth	Gum Arabic	168	1.95	0.21	0.002
	Control	151	1.85	0.36	

Figures

Figure 1

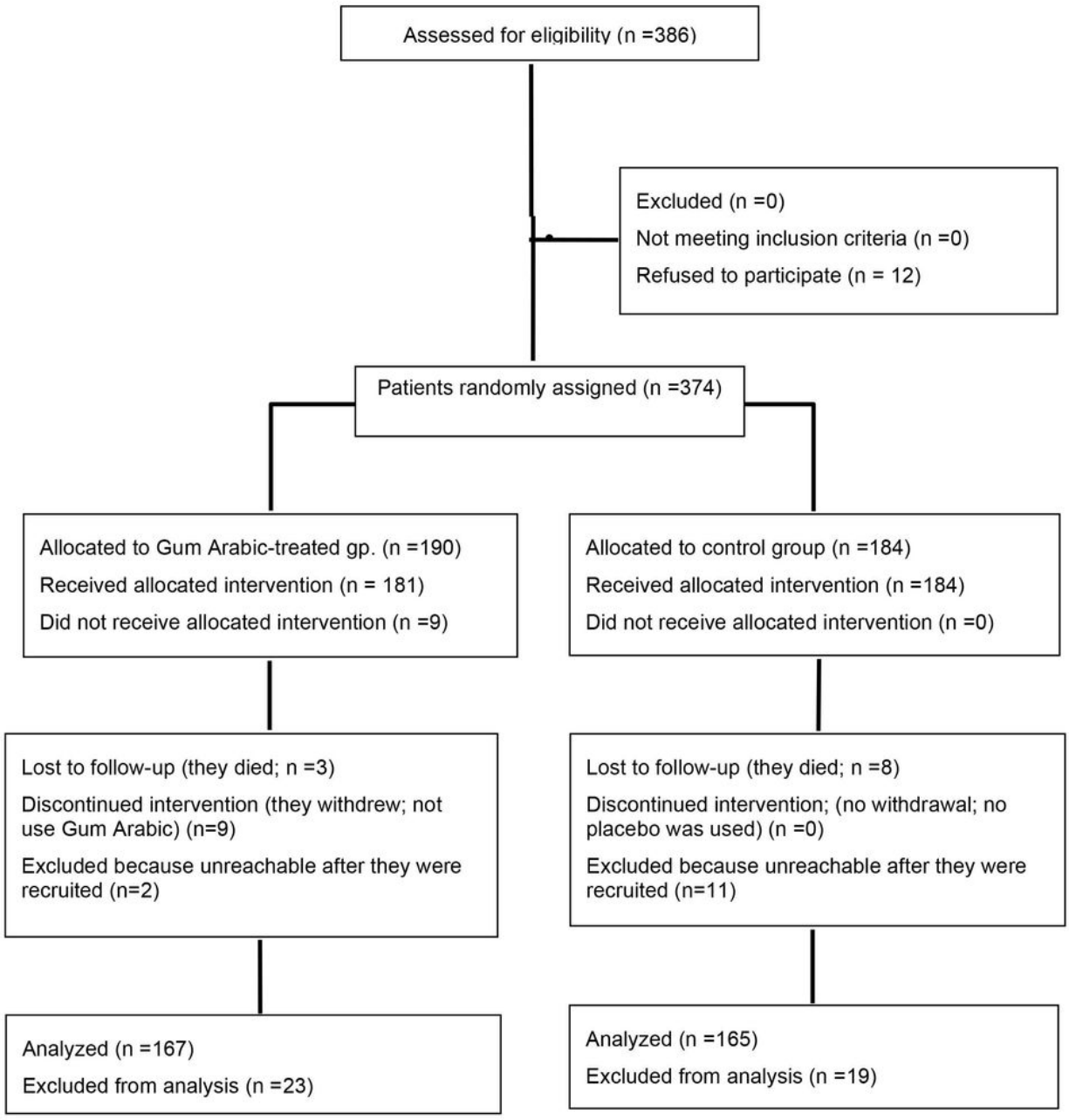

Figure 1

CONSORT Flow the participants throughout this study.

Figure 2

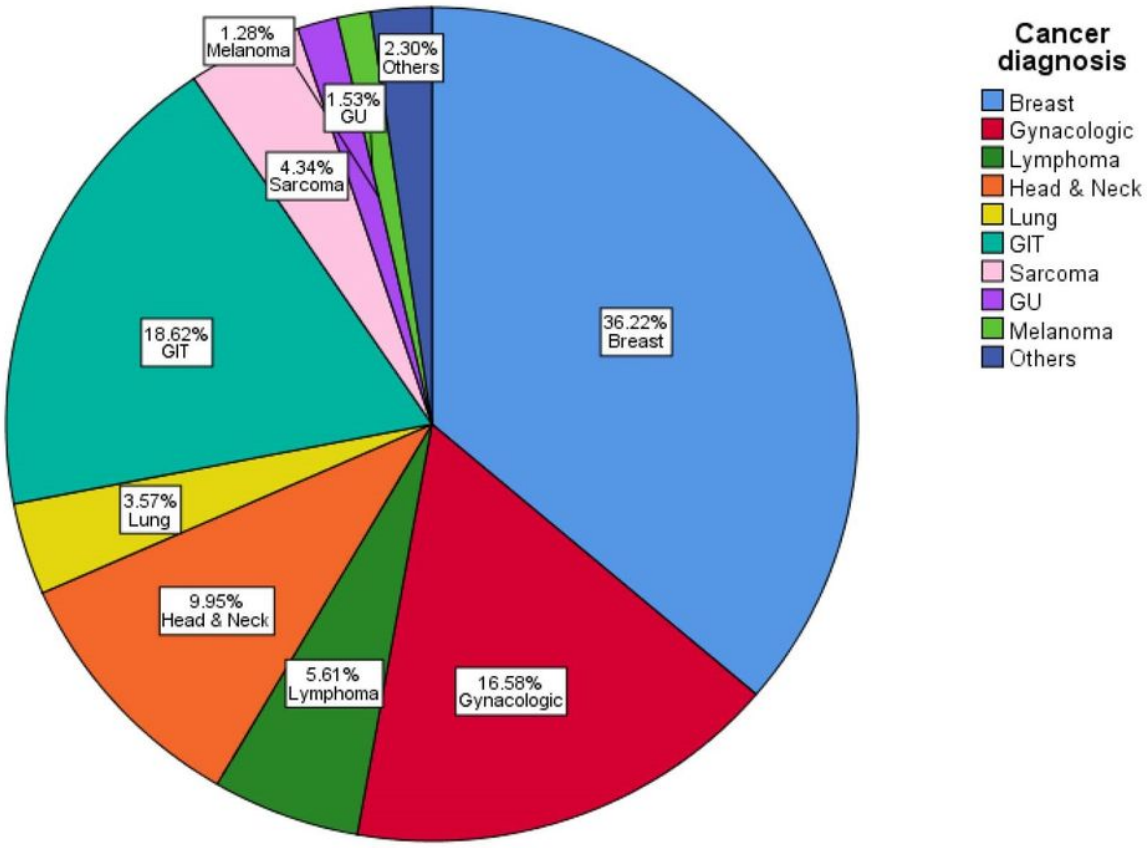

Figure 2

Distribution of cancer types among the 392 patients. GI: gastrointestinal; GU: genitourinary; Others: backbone, bronchus, carcinoid, esophagus, mesothelioma, mycosis fungoides, pseudomyxoma, pyriform, rectum, spinal, anal, bowel, colon, colorectal, soft tissue sarcoma etc...

Figure 3

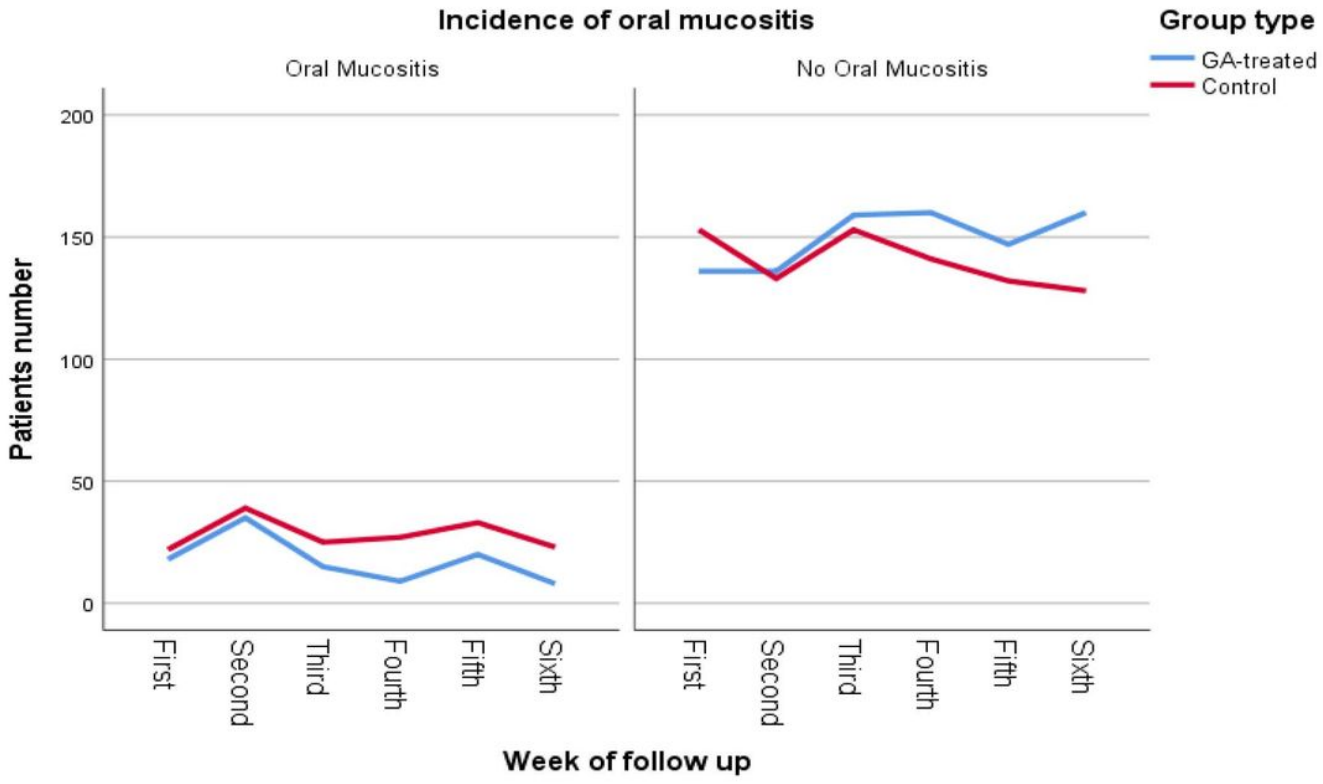

Figure 3

Oral mucositis incidence during the six weeks in the two groups.

Supplementary Files

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