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Original Article

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The effect of three mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies: A randomized control trial

ABSTRACT

Aims: The present study was done to assess the effect of three alcohol-free mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies.

Materials and Methods: Eighty patients with head and neck malignancies, scheduled to undergo curative radiotherapy, were randomly assigned to receive one of the three alcohol-free test mouthwashes (0.12% chlorhexidine, 1% povidone-iodine, or salt/soda) or a control. The patients were instructed to rinse with 10 ml of the mouthwash, twice a day, for a period of 6 weeks. Mucositis was assessed at baseline and at weekly intervals during radiation therapy, using the World Health Organization criteria for grading of mucositis. The baseline demography of the four groups was matched for age, sex, stage of cancer, and whether the patient had cancer of oral or extraoral regions. A *post hoc* test for repeated measures was used to find the difference of mean mucositis scores between the groups at various week intervals.

Results: Among the 76 patients who completed the study, patients in the povidone-iodine group had significantly lower mucositis scores when compared to the control group from the first week of radiotherapy. Their scores were also significantly lower when compared to the salt/soda and chlorhexidine groups from the fourth and fifth week, respectively, after radiotherapy.

Conclusions: This study demonstrates that use of alcohol-free povidone-iodine mouthwash can reduce the severity and delay the onset of oral mucositis due to antineoplastic radiotherapy.

KEY WORDS: Alcohol-free mouthwashes, head and neck malignancies, radiation-induced oral mucositis

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Patients with cancer in the head and neck area can be treated with surgery, radiotherapy, or a combination of both. A well-known side effect of radiation is mucositis.[1] Floyd[2] had defined oral mucositis as the inflammatory change of the oral mucosa resulting from the direct effect of radiotherapy. According to Beumer *et al*.,[3] inhibition of cell growth and maturation by radiation disrupts the primary mucosal barrier of the mouth and throat and thereby creates a pathway for the establishment of oropharyngeal infection by resident oral microflora. The consequences of this include oral mucositis and gingivitis, oral candidiasis, xerostomia, trismus, dental caries, osteoradionecrosis, cellulitis, and viral mucosal eruptions. These oral complications may cause significant patient discomfort and lead to poor nutrition; it may also be responsible for delays or dosage limitations in antineoplastic treatments. In addition, severe mucositis may require temporary or permanent cessation of radiation therapy before completion of the planned radiation therapy program. This is of marked concern, as there is strong clinical and radiobiologic evidence that protraction of overall treatment time has adverse influences on the radiocurability of certain human tumors, particularly squamous cell carcinoma of the head and neck region.[4]

Various agents are used in order to reduce the incidence and severity of oral mucositis. Sodium bicarbonate has an immediate effect in reducing the acidity of oral fluids; it dilutes accumulating mucus and discourages colonization by yeast. Chlorhexidine gluconate is an antimicrobial agent that appears to be effective in controlling early periodontal infections. Hydrogen peroxide, once recommended as an oral rinse to aid in the management of adhesive mucus and the oxygenation of the oral tissues, has recently come into disrepute because of its possible carcinogenic and antifibroblast, healing-delaying action.[5] Povidone-iodine also appears to be beneficial in controlling radiation-induced oral mucositis.[6,7]

An ideal oral rinse for patients with head and neck malignancies should reduce the oral microflora,

promote reepithelization of soft tissue lesions, normalize the pH of oral fluids, have an acceptable taste, and be nontoxic.[5] An earlier study has reported that alcohol-free mouthrinses cause less patient pain than those containing alcohol.[8]

The development and use of alcohol-free mouthrinses is relatively new. Certain studies have shown their efficacy and lack of side effects, but there is no clear evidence.[8] The present study was done to find out the effect of three alcohol-free mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies.

MATERIALS AND METHODS

The present study was a double-blind, placebo-controlled, randomized clinical trial. After the approval of the study protocol by the Institutional Ethics Committee, Manipal University, official permission to conduct the study was obtained from the Department of Oncology, KMC Attavar Hospital, Mangalore, India.

Eighty patients with head and neck malignancies, scheduled to undergo radiotherapy at KMC Attavar Hospital, Mangalore, were enrolled in the present study and randomly assigned to the test or control groups (20 patients each). The inclusion criteria were as follows:

1. Patient should be above 18 years of age.
2. Patient should have head and neck malignancies of stage II to stage IV, according to TNM classification.
3. Patient should be scheduled to receive radiotherapy at the Department of Oncology, KMC Attavar Hospital, Mangalore, India.
4. The planned radiation dose should be equal to or exceed 60 Gy, delivered in 30 fractions, over a 6-week period.
5. At least one-third of the oral cavity mucosa should be included in the radiotherapy field.
6. Patient should be able to read and/or understand and sign the consent form.

The exclusion criteria were as follows:

1. Patients with open mouth sores at study entry.
2. Patients who had undergone prior radiotherapy or chemotherapy.
3. Patients with HIV infections, diabetes mellitus, or hyperthyroidism.
4. Patients having allergy to iodine or povidone-iodine.
5. Patients using any other prophylactic mouthwashes.
6. Patients who were pregnant and/or nursing.
7. Patients who required use of any form of treatment/ medicaments (e.g., antibiotics, analgesics, etc.) during the course of radiotherapy because of exacerbation of symptoms.

All patients who participated in this study received external bilateral irradiation from a cobalt-60 radioactive source that emits gamma rays at an average energy level of 1.2 MeV. All the study participants received 2 Gy of therapeutic radiation daily, up to a total dose of 60 Gy; the doses were given 5 days a week over a period of 6 weeks. Radical resection or debulking of the primary tumor often preceded the course of irradiation.

The effect of three test mouthwashes and a control were assessed in the present study. The mouthwashes assessed were:

1. 0.12% Chlorhexidine
2. 1% Povidone-iodine
3. Salt/sodium bicarbonate
4. Plain water (control).

Ingredients like coloring agents, sweeteners, and flavoring agents were added to the mouthwash so that all of them had an identical color and an acceptable taste. All the mouthwashes were alcohol free and were prepared at KMC Pharmacy, Manipal, India. The mouthwashes were numbered randomly from 1 to 80 by the mouthwash manufacturer (Dispensing Wing, KMC Pharmacy, Manipal, India). The coding was done by the manufacturer and was known only to him. It was revealed to the investigator only at the end of the study. Mouthwashes were dispended in identical 500 ml coded glass bottles having a lid that could be used for measuring out 10 ml doses.

After obtaining informed consent, the patients were numbered from 1 to 80 and randomly assigned to one of the four groups. A patient assigned a particular number was given the mouthwash with the same number. Once the mouthwash was over it was replaced with the same numbered mouthwash.

The patients were instructed to rinse their mouth with 10 ml (measured by the bottle lid) of the mouthwash, twice a day, for a period of 6 weeks. They were asked to swish the mouthwash for about 2 min and then expectorate. They were requested to do the above after food and to abstain from eating or gargling the mouth for half an hour after use of mouthwash. The patients were initially dispensed a 500 ml bottle; a second bottle was given after the third week. A flowchart explaining the methodology and allocation of subjects into the various treatment and control arms of this clinical trial is shown in Figure 1.

Patient compliance was assessed by weekly checking of the level of mouthwash left in the bottle. Mucositis was assessed at baseline and at weekly intervals during radiation therapy, using the World Health Organization criteria for grading of oral mucositis.[9-11] A single calibrated examiner carried out the assessments. Calibration was done to reduce intraexaminer variability. Kappa statistics was also performed to find out the intraexaminer variability and was found to be acceptable (kappa value = 0.85).

Statistical analysis

The results were analyzed using SPSS for Windows, version 10.0.

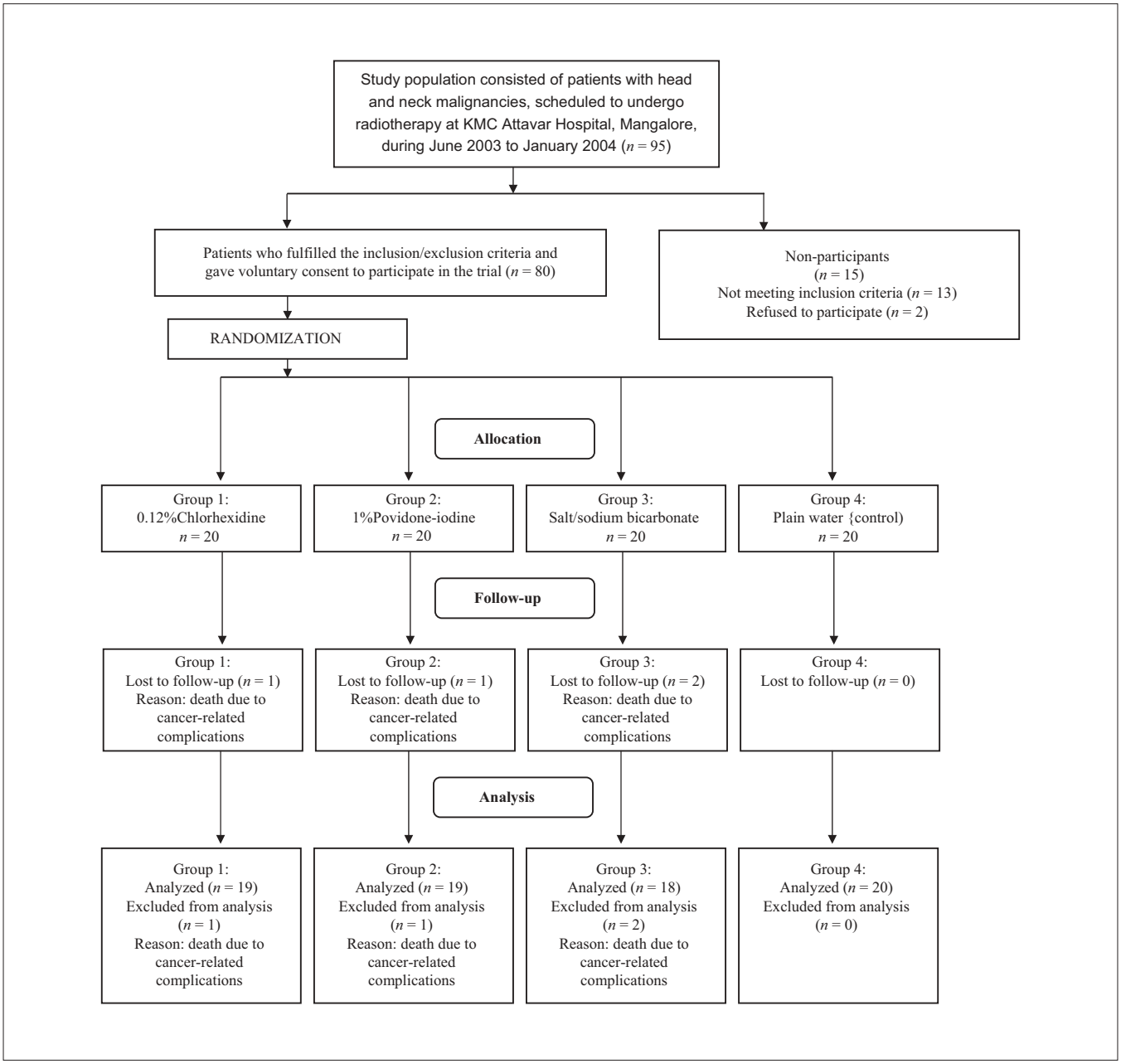

Figure 1: Flowchart of the randomized control trial

The null hypothesis for the current study was that there would not be any difference between the test groups and the control in the onset and severity of radiation-induced oral mucositis in patients with head and neck malignancies.

The primary endpoint of the study was at the end of the sixth week, after the termination of radiotherapy for patients with head and neck malignancies.

Further, the present trial was designed to have a power of 90% and alpha level of significance (type 1 error) was fixed as 0.05, i.e., the null hypothesis was rejected if the *P* value was less than this value. The standard difference in the mean mucositis scores between the test and the control arms was assumed from an earlier study[12] as 1.14. However, the standard difference in the mean mucositis scores between the test arms was considered negligible in the present trial. Lehr's formula[13] was used to calculate the sample size for a power of 90% and a two-sided significance level of 0.05.

The baseline demography of the four groups was matched for age, sex, stage of cancer, and whether patients had cancer of oral or extraoral regions. Quantitative data was assessed using ANOVA, while the categorical data were analyzed using the chi-square test. A *post hoc* test for repeated measures was used to find the difference of mean mucositis scores between the groups at various week intervals.[14]

RESULTS

Of the total 95 patients who reported to Department of Oncology, KMC Attavar Hospital, Mangalore, India, during July 2003 to January 2004 for treatment of head and neck malignancies, 80 patients, who fulfilled the inclusion/exclusion criteria, participated in this trial and were randomly allocated into one of four groups. Among them, four patients (one in the chlorhexidine group, one in the povidone-iodine group, and two in the salt/soda group) died during the trial period due to tumor-related complications. All the 76 patients who completed the trial complied with the instructions given to them.

Table 1 shows the distribution of patients in the four groups based on age, sex, location of cancer, and stage of cancer. No statistically significant difference was seen among the four groups.

Table 2 shows the mean mucositis scores of the patients in the four groups at weekly intervals. A significant difference in the mean mucositis scores was observed among all the four groups. When a *post hoc* analysis for repeated measure was used for analysis, a statistically significant difference was observed between the povidone-iodine group and the control group ($P = 0.013$) at the end of the first week. At the end of the second week, in addition to the povidone-iodine group, the chlorhexidine and salt/soda groups also differed significantly from the control group. At the end of the fourth week, a significant difference was also observed between the povidone-iodine and salt/soda group ($P = 0.016$). The fifth week values showed a significant difference not only between all the test groups and the control group, but also within the test groups. Values after the sixth week showed a slightly different trend: though there was a significant difference between the povidone-iodine group and all the other groups, the difference in mean mucositis scores among the other groups were not statistically significant. The patterns of mucositis among the test and control groups at weekly intervals are shown in Figure 2.

Figure 3 shows the distribution of patients among the four groups based on the onset of mucositis. Onset of mucositis was defined in the present trial as the time when the patient showed first evidence of mucositis. Among the 40 patients who had mucositis onset at the first week, 17 belonged to the control group while only 6 belonged to the povidone-iodine group. Five patients in the povidone-iodine group had mucositis onset in the third week and two patients in the same group had onset of mucositis after the third week. A chi-square analysis showed a statistically significant

Table 1: Distribution of patient characteristics in four groups based on age, sex, location, and stage of cancer

	Chlorhexidine	Povidone-iodine	Salt/soda	Control
Age	57.35	54.25	58.20	54.45
Sex				
Male	13	16	15	19
Female	6	3	3	1
Location				
Oral	9	7	8	7
Extraoral	10	12	10	13
Stage				
Stage III	10	9	8	9
Stage IV	9	10	10	11

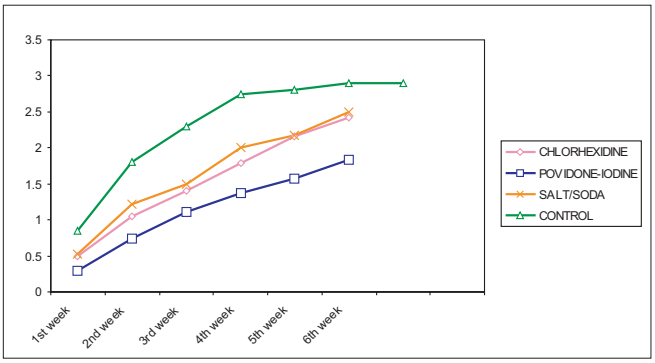

Figure 2: Distribution of mean mucositis scores at weekly intervals for patients in the four groups.

Table 2: Distribution of patients in the four groups based on mean mucositis score at weekly intervals

Groups	1st week	2nd week	3rd week	4th week	5th week	6th week
Chlorhexidine group						
Mean	0.50	1.05	1.40	1.79	2.16	2.42
SD	0.61	0.22	0.50	0.42	0.60	0.61
Povidone-iodine group						
Mean	0.30	0.74	1.11	1.37	1.58	1.84
SD	0.47	0.65	0.57	0.68	0.69	0.76
Salt/soda group						
Mean	0.53	1.22	1.50	2.00	2.17	2.50
SD	0.61	0.65	0.71	0.69	0.62	0.51
Control group						
Mean	0.85	1.80	2.30	2.75	2.80	2.90
SD	0.37	0.70	0.73	0.64	0.62	0.45
Total						
Mean	0.54	1.21	1.58	1.99	2.18	2.42
SD	0.55	0.69	0.77	0.79	0.76	0.70
ANOVA	3.793	11.442	11.804	17.263	12.112	10.434
P	0.014	0.000	0.000	0.000	0.000	0.000

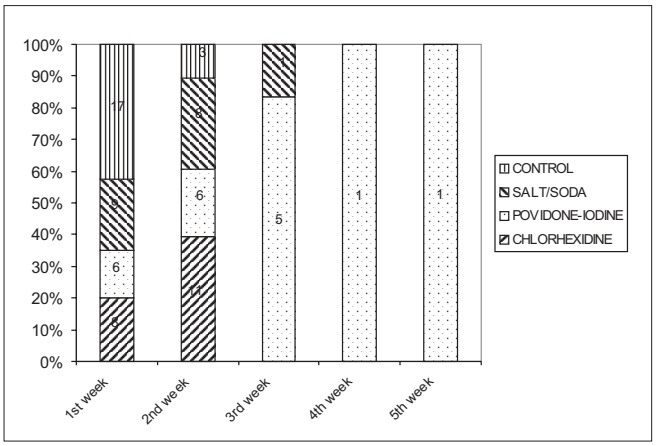

Figure 3: Distribution of patients among the four groups based on the onset of mucositis

difference between the onset of mucositis among the groups ($X^2 = 28.321$; $P = 0.005$).

DISCUSSION

The present study was done to find out the effect of three alcohol-free mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies. It is predictable that radiotherapy for head and neck malignancies will result in oral mucositis when the oral mucosa is included in the treatment field. Radiation-induced oral mucositis and its symptomatic management can serve as a model for mucosal disruptions resulting from other causes. Therefore, the findings of this trial may have implications for the management of mucositis resulting from causes such as radiotherapy, chemotherapy, trauma, infection, and oral dermatoses.[15]

The present study demonstrated that rinsing with povidone-iodine reduced the incidence and severity of radiation-induced oral mucositis, when compared to chlorhexidine, salt/soda, and control mouthwash. Rahn et a.l[6] and Adamietz *et al*.[7] had shown that rinsing with povidone-iodine, in addition to a standard prophylaxis regimen, reduced the incidence, severity, and duration of radiation-induced oral mucositis.

Oral mucositis during radiation therapy is caused by various factors. Oral microorganisms are important for producing infections of the oral mucosa and antiseptic agents may decrease the incidence and severity of these infections by reducing the number of these microorganisms. Hence, povidone-iodine can be very useful; it has good *in vitro* microbicidal efficacy against some bacteria, fungi, protozoa, and viruses. The antibacterial efficacy of povidone-iodine *in vivo* against oral bacteria is established. It is supposed that antiseptic efficacy may cause a reduction in the severity of oral mucositis. In contrast to other antiseptic agents, povidone-iodine does not lead to any irritation or damage of the oral mucosa, even when rinsing is performed over a prolonged period of 8-10 weeks.[6]

Another well-known and economical antiseptic agent, chlorhexidine, was not found to be as effective as povidone-iodine in the present study. In their studies, Spijkervet *et al*.[16] and Ferretti *et al*.[12] observed little or no reduction of mucositis in patients receiving high-dose head and neck radiotherapy when chlorhexidine was used as a mouthwash. Foote *et al*.,[17] in his study, showed slightly more stomatitis and side effects in patients using chlorhexidine, thus ruling out the possibility that chlorhexidine can lower the average daily mucositis score. Epstein *et al*.[18] demonstrated little effect on lactobacillus count after use of chlorhexidine rinse in patients receiving cancer radiotherapy.

The lack of effect of chlorhexidine mouthwash in patients undergoing radiotherapy may be explained by the observation that the chlorhexidine molecule, a divalent cation, probably does not bind directly to epithelial tissues but rather binds to the negatively charged salivary mucins or glycoproteins. *In vitro* evidence further supports the concept that salivary glycoproteins are necessary cofactors for mucosal cell protection by chlorhexidine. Severe persistent xerostomia develops in patients receiving high-dose radiation therapy rather quickly (within 14-21 days) after the initiation of radiation therapy, thus depriving oral epithelial tissues of their usual coating of salivary fluids and diminishing the effect of chlorhexidine in these patients.[12] However Toljanic *et al*.,[19] in his study on six subjects, showed that 0.12% chlorhexidine was retained in the oral cavity for atleast 4 h after a single rinsing and that the property of substantivity remains active in spite of radiation-induced changes in the oral cavity and salivary glands. Samaranayake *et al*.[20] suggested the use of chlorhexidine rinse, rather than benzydamine mouthwash, in patients undergoing postoperative radiotherapy for squamous carcinoma of the oral cavity, as the former caused less oral discomfort.

The effect of a salt/soda mouthwash was also assessed in the present study. Saline solution is thought to aid in the formation of granulation tissue and to promote healing. Saline solution mouthwashes are safe and economical and have been used in cancer patients.[21] Normal saline gargles cleanses the wounds, reduces swelling, and can decrease pain.[22] Sodium bicarbonate has also been used as a cleansing agent because of its ability to dissolve mucus and loosen debris. The combination of salt and sodium bicarbonate raises oral pH and prevents overgrowth of aciduric bacteria.[21] In the present study, salt/soda mouthwash was not found to be as effective as povidone-iodine, though it was more effective than the control mouthwash. Feber,[23] in his study, concluded that management of mucositis due to oral irradiation was better with saline than with hydrogen peroxide rinses. Dodd *et al*.[24] suggested than since there is no significant difference in efficacy between micronized sucralfate and salt and soda, use of the less costly salt and soda is prudent and cost-effective. However, Carl and Emrich[5] showed that grade 3 mucositis developed more often in patients who used conventional oral care with 5% sodium bicarbonate, saline, and 3% hydrogen peroxide.

Studies have shown that the frequency of mucositis is high in patients treated with radiotherapy, affecting 100% of patients overall.[9] In the present study also, all the patients (76 patients) who completed the trial developed some degree of mucositis. The onset, intensity, and duration of mucositis varies with the individual but most often starts in the second week of therapy or after a dose of about 2000 cGy.[25] More than 50% of the patients (40 patients) in the present trial developed mucositis in the first week after radiotherapy, while another 28 developed mucositis after 2 weeks of therapy. The range for onset of mucositis was 1-2 weeks for the chlorhexidine and the control groups, 1-5 weeks for the povidone-iodine group, and 1-3 weeks for the salt/soda group. These results were comparable with the studies done by Rahn *et al*.[6] and Adamietz *et al*.,[7] where the onset of mucositis was in the range of 1-4 weeks in the povidone-iodine and in the range of 1-3 weeks in the control group. The onset of mucositis was significantly low in the povidone-iodine group when compared to the control group, similar to the findings of Rahn *et al*.[6] and Adamietz *et al*.[7]

CONCLUSION

This study demonstrates that the use of alcohol-free povidone-iodine mouthwash can reduce the severity and delay the onset of oral mucositis due to antineoplastic radiotherapy, thus improving the quality of life for patients. Hence, use of alcohol-free povidone-iodine mouthwash can be advocated for patients' use during radiotherapy. However, these results warrant further evaluation in a randomized study with a larger number of patients.

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