Investigation of persica mouth wash versus doxepin 0.5% oral rinse for chemo-radiotherapy-induced mucositis pain in the treatment of head and neck cancers, a randomized double blind clinical trial

Pegah Mahjour

Shahid Sadoughi University of Medical Sciences and Health Services

Hassanali Vahedian Ardakani

Shahid Sadoughi University of Medical Sciences and Health Services Yazd Research and Clinical Centre for Infertility

Mohsen Nabi Meybodi

Shahid Sadoughi University of Medical Sciences and Health Services Yazd Research and Clinical Centre for Infertility

Masood Shabani

Shahid Sadoughi University of Medical Sciences and Health Services Yazd Research and Clinical Centre for Infertility

Farahnaz Pouyanfar

Shahid Sadoughi University of Medical Sciences and Health Services Yazd Research and Clinical Centre for Infertility

Behrooz Heydari (✉ B.heydari@ssu.ac.ir)

<https://orcid.org/0000-0003-3497-1879>

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Abstract

Background: One of the common side effects of radiotherapy and chemotherapy in patients with head and neck cancer is oral mucositis. This painful complication restricts the ability to eat and drink and increases the risk of oral infections. The aim of this study was to investigate the effect of doxepin oral rinse 0.5% in comparison with persica mouthwash on reducing the pain of oral mucositis in patients with head and neck cancer after radiotherapy and chemotherapy.

Methods: This clinical trial was performed on 56 patients admitted in the oncology ward of Shahid Sadoughi Hospital and Shahid Ramezanzadeh radiotherapy center in Yazd, who received more than 45 gray of radiation and had mucositis and their pain score was more than 4 on the basis of the Visual Analogue Scale (VAS). Patients were randomly divided into two groups of persica and doxepin 0.5%. The data collection tool was a questionnaire including visual analogue scale for pain, taste satisfaction and possible complications. Data were analyzed by using SPSS19 software and Chi-square test.

Results: There was no significant difference between the mean score of pain in doxepin and persica groups 5,15,30, 120,240 minutes and 24 hours after taking the mouthwash; just in the doxepin group, the mean of pain reduction 60 minute after taking the mouthwash was higher than persica group ($P > 0.05$). There was no significant difference between the mean score of burning sensation in doxepin and persica groups 30,60,120,240 minutes and 24 hours after taking the mouthwash; just in the persica group, the mean of burning sensation reduction 5,15 minutes after taking the mouthwash was lower than doxepin group. The level of taste satisfaction and drowsiness in the doxepin group was significantly higher than persica group. ($P > 0.05$)

Conclusion: Persica mouthwash, like doxepin mouthwash, was effective in reducing the mucositis pain in patients and just in the doxepin group reduction in pain after 60 minutes was higher than persica group

Background

Mucositis is a painful inflammation in the gastrointestinal tract (1, 2), Symptoms of oral mucositis include burning sensation, ulcers, pain and discomfort when swallowing. Sometimes patients, need placement of a nasogastric tube (NG tube) to prevention of dehydration and malnutrition.(2, 3)

Supportive care and treatments, as well as the restriction of aggressive therapies and planned techniques of radiotherapy and chemotherapy, can decrease severities of mucositis(3).

The main cause of mucositis is not known, but direct damage to mucosa during radiotherapy and chemotherapy and epithelial disorder is important (1). major risk factors include volume of mucosa that receives radiation, the intensity of the treatment and underlying disease(3).

Many studies have been conducted aimed at reducing the pain of oral mucositis, including the use of amphotericin, gelclair (polyvinyl pyrrolidone sodium), which have shown good results, however, FDA has not yet introduced an effective medication (3–5).

Doxepin shows its analgesic effect when is applied topically(6). Doxepin analgesic effect is due to its suppressive effect on cutaneous pain receptors which acts as a sodium receptor blocker. Also, doxepin can regulate spinal cord pain by attaching to N-methyl D-aspartate receptors(6).

Persica herbal mouthwash contains alcoholic extract of *salvadora persica*, mint, and yarrow. *Salvadora persica* contains fluoride, isothiocyanate, vitamin C, silica, resin, calcium salts, chloride, tannin and tannic acid. Isothiocyanate releases cyanide in contact with saliva and prevents the growth of bacteria in the mouth(7, 8). Several studies reported that persica mouthwash had anti-plaque, anti-hemorrhage, anti-ulcer, analgesic, anti-microbial and anti-inflammatory effects(9–14). The precise analgesic mechanism of persica is unclear, but since in clinical trials effect of *Salvadora Persica* has been neutralized by naloxone, its effect may be applied through opiate receptors(15).

According to the studies on doxepin and its analgesic effects, the current study investigates the effect of oral doxepin 0.5% in comparison with persica mouthwash on reducing the pain of oral mucositis in patients with head and neck cancer after radiotherapy and chemotherapy.

Methods

Patients

This randomized double blind parallel clinical trial study was conducted in the oncology department of Shahid Sadoughi Hospital and Shahid Ramezanzadeh radiotherapy center from May 2018 to June 2019 in Yazd. From 80 patients, 56 eligible patients were assigned to study groups. After confirming the diagnosis of mucositis by the physician, the grade of mucositis was determined using the World Health Organization (WHO) criteria: grade 0-no changes, grade 1- soreness erythema, grade 2- oral erythema, ulcers, solid diet tolerated, grade 3- oral ulcers, liquid diet only, grade 4- oral alimentation impossible(16). Patients with mucositis who received chemotherapy or more than 45 radiation gray and had a pain score more than 4 basis on the visual analog scale (zero lowest pain and 10 most pain) and were older than 18, were included in the study, exclusion criteria were age younger than 18, usage of TCA or MAOi in the last 2weeks, history of TCA sensitivity,untreated urinary retention in the last 6 weeks, untreated open-angle glaucoma, candidiasis infection or oral herpes.

Patients' information such as age, sex, weight, underlying diseases and other medications used by them were recorded.

Study design

Patients were randomly divided into two groups by using Random.org site, According to a

study on the effectiveness of doxepin compared to a placebo(17) the sample size needed in this study was calculated by using the cochrane formula, A total of 25 people are required in each group. Considering 10% of the sample loss, the number of patients will be 28 per group. to receive doxepin 0.5% or persica mouthwash. Dr Pegah Mahjour generated the random allocation sequence, and enrolled participants, and Dr Behrooz Heydari assigned participants to interventions ,the mouthwash was given to each patient by care providers,none of them knew the content of the mouthwash.both groups received the mouthwash with the same conditions. At the first step, initial pain was determined and then patients in each group gargled 5 cc of the solution for 1 minute (3 times a day). level of pain in the mouth, burning sensation, inappropriate taste, drowsiness and any possible side effects were recorded respectively 5, 15, 30, 60, 120, 240 minutes and 24 hours after taking mouthwash.

Patients should refrain from eating and drinking an hour before and one hour after taking mouthwash.

Patients who could not tolerate the pain, were allowed to use acetaminophen 500 mg (at least 4 grams per day); however, the interval between analgesic use and the solution should be at least 60 minutes.

Data gathering

clinical information of patients were recorded at the initiation of the study.

The mean of pain intensity was measured by VAS. The mean of burning sensation were assessed by VAS (0 lowest pain and 10 most pain).

SPSS V.19 software was used to statistical analysis of data. According to the normal distribution of data, chi-square tests were used to compare the results. The significance level was considered less than 0.05.

Results

out of 56 patients(each group N=28), 35.7% (N=20) were male. The mean age of the patients was 55.5 ± 14.44 years. In the persica treatment group 32.1% were male and in doxepin treatment group 39.3% were male. The mean age of patients in persica and doxepin treatment group was 53.5 ± 13.83 and 57.58 ± 78.8 years respectively. The distribution of patients in terms of age and sex was not statistically significant in two groups ($P < 0.05$).

The mean of pain intensity before the intervention in the persica treatment group was 6.64 ± 1.19 and in doxepin treatment group was 7.23 ± 1.42 , although this difference was not statistically significant ($P = 0.083$).

There was no significant difference in pain severity in the persica and doxepin groups at 5, 15, 30, 120, 240 minutes and 24 hours after use of the solutions (P -value < 0.05) (Table 1 (but patients in doxepin

group reported less pain score at 60 minutes after taking the solution. (P-value=0.038).

The mean of burning sensation in persica group was greater only 5 and 15 minutes after taking the solution than doxepin group (P value =0.000), and there was no significant difference in the mean of burning sensation score between the two groups at other times (P <0.05) (Table 2).

On the otherend, in terms of adverse effect, the level of drowsiness in the doxepin group was remarkably higher than the persica group. (P-value=0.000) but taste of doxepin mouthwash was better than persica (P= 0.000) (Table 3).

Discussion

Regarding the problems and complications of oral mucositis, prevention and treatment of this complication in patients undergoing chemotherapy and head and neck radiotherapy is very important.

Timely treatment of this condition will relieve pain, improve nutrition, reduce the need for analgesics, antimicrobials and increase the patient's ability to tolerate the treatment, and thus it will raise the life expectancy of the patients.

The aim of this study was to investigate the effect of doxepin 0.5% mouthwash in comparison with perisca mouthwash on reducing the pain of oral mucositis in patients with head and neck cancer after radiotherapy and chemotherapy.

This randomized controlled trial resulted in both mouthwashes decreased pain score of mucositis during the study. This study has shown that doxepin had better taste but led to drowsiness. Doxepin reduces pain through Na channel blocking and NMDA receptors regulating. The precise analgesic mechanism of persica is unclear, but since in clinical trials effect of *Salvadora Persica* has been neutralized by naloxone, its effect may be applied through opiate receptors.

Recent studies against this study have focused on persica's effectiveness in preventing mucositis. For example, the results of a study by Zakaria and Abdul Rahim showed that saladora persica blue extract reduced the incidence of mucositis caused by 5FU in rats (18). In a study by Abedipour et al aiming at comparing the effect of persica and chlorhexidine mouthwash on preventing mucositis in 30 patients aged 14–50 years with acute myeloblastic leukemia and acute lymphoblastic leukemia under chemotherapy showed that persica and chlorhexidine mouthwash were equally effective in preventing stomatitis. The researches recommended persica, regarding the side effects of chlorhexidine (19).

In a study conducted by Hoor and Ahmed et al with the aim of investigating the analgesic effect of persica at doses of 700,500,300 mg / kg in compare with aspirin on 21 mice, it was concluded that persica would be effective in reducing the pain at doses of 500 and 700 mg / kg after 210 minutes (20).

The aim of this study was to investigate the effect of doxepin mouthwash in comparison with perisca mouthwash on reducing the pain of oral mucositis.

In 2001, Epstein et al conducted a study to evaluate pain relief from oral mucositis after oral use of doxepin 0.5% in cancer patients. Researchers evaluated oral pains before taking mouthwash and 4 hours after it by Visual Analog Scale (VAS). In more than 50% of patients, pain relief was observed more than 3 hours after taking mouthwash, and this pain reduction did not return to the initial level until the end of 4 hours.

In the current study, the pain did not return to the initial level until the end of 24 hours.

Also, this oral mouthwash had acceptable taste from the viewpoint of patients and they did not report burning sensation which was consistent with the result of present study (21).

In a study by Epstein et al in 2006, aiming at examining the analgesic effect of doxepin 31.4%, patients reported inappropriate feelings and mild burning, which has not been reported in the present study(22).

The results of this study showed that pain induced by mucositis decreased by using doxepin, which were consistent with study by Epstein et al (22) and Leenstra et al (17). Study of Epstein et al (22) evaluated the analgesic effect of doxepin 5 mg / ml on 51 patients by using it 4 times and the study of Leenstra et al (17) was performed on 55 patients to compare the effect of using doxepin and placebo in a single dose and pain level was measured at 5, 15, 30, 60 and 120 minutes. According to the findings of this study it seems that dexpine mouthwash play a very effective role in mucositis pain control.

Also, in the persica group, pain decreased after 30 minutes, then reached the plateau and did not return to the base after 4 hours. Patients used mouthwash two more times in a day and pain did not return to the initial level for 24 hours.

Comparison of the two groups showed that the analgesic effect did not differ significantly in 5, 15, 30, 120, 240 minutes and 24 hours later in both groups, and persica could reduce pain in the patients.

It is worth noting that reduction of mucositis pain in both groups was significant in favor of doxepin at 60 minutes.

This is probably due to the anesthetic effect of doxepin mouthwash, which lasted about one hour in patients. After eliminating the anesthetic effect of doxepin mouthwash, the analgesic effects of the two groups were not significant at 120 and 240 minutes.

The burning sensation in the doxepin group was significantly higher than persica group at 5 and 15 minutes.

In the current study, patients in doxepin group did not report change in their taste after 4 hours, which indicates that the analgesic effect of this drug was not due to local anesthesia. This conclusion was confirmed by the study of Epstein et al(23). Patients in the persica group also did not report a change in their taste, which was contrary to the results of the Salehi study, which 40% of the patients reported change in their taste(19).

The possible cause of this different might be related to the duration of the use of persica, which was 4 weeks in the study of Salehi and it was only 1 day in the current study.

In this study 50% of patients in doxepin group suffered from severe drowsiness and 49.4% of them reported mild drowsiness. This conclusion was confirmed by the study of Epstein et al(21–23); patients in persica group did not report this condition.

Despite the introduction of various drugs and methods, there is no standard treatment for oral mucositis (24). But according to the findings of this study, mentioned mouthwashes had beneficial effects in the control of oral mucositis.

This study had several limitations such as finding sufficient number of patients due to pursuing critically ill patients.

Conclusion

Persica mouthwash, like doxepin mouthwash, was effective in reducing the mucositis pain in patients and just in the doxepin group reduction in pain after 60 minutes was higher than persica group.

Abbreviations

VAS: Visual Analog Scale

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Yazs University of Medical Sciences, Iran (approval no. IR.SSU.MEDICINE.REC1396.200) and it also approved by Iranian Registry of Clinical Trials (approval no. **IRCT20181208041882N1**). All patients signed an informed consent form prior to participation in the study.

Consent for publication

Consent for publication was agreed upon in the written consent forms signed by the patients.

Availability of data and materials

Please contact the author Behrouz Heydari (B.heydari@ssu.ac.ir) upon reasonable requests.

Competing interests

The authors declare that they have no competing interests regarding the publication of this paper.

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Autours' contributions

BH has designed, conducted the manuscript; PM did the experiments and finished the manuscript; HV, MS,FP and MN have supported the experiment design and implementation, All authors read and approved the final version of the manuscript and ensure this is the case.

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Tables

Table 1: The mean score of pain in 8 measured times in the two groups

Group	Persica (Mean ± SD)	Doxepin (Mean ± SD)	Total (Mean ± SD)	P-value
Measured times				
0 min	1.19±6.64	1.42±7.23	1.43± 6.94	0.105
5 min	1.50±5.89	1.42±5.64	1.91±5.77	0.630
15 min	2.35±4.71	2.59±4.25	2.46±4.48	0.486
30 min	2.41±3.93	2.59±3.07	2.50±3.50	0.203
60 min	2.54±3.61	2.22±2.55	2.46±2.93	0.038
120 min	2.63±3.43	2.14±2.25	2.51±2.79	0.055
240 min	2.75±3.21	2.07±2.17	2.42±2.64	0.082
24 hours	2.82±3.11	1.86±1.97	2.48±2.94	0.060

Chi-Square test

Table 2: The mean of burning score in 7 measured times in the two groups

Group Measured times	Persica (Mean $\pm$ SD)	Doxepin (Mean $\pm$ SD)	Total (Mean $\pm$ SD)	P-value
5 min	2.69 $\pm$ 5.32	0.75 $\pm$ 2.31	3.39 $\pm$ 3.40	0.000
15 min	3.15 $\pm$ 3.96	0.75 $\pm$ 2.32	2.36 $\pm$ 3.18	0.000
30 min	2.62 $\pm$ 1.50	0.57 $\pm$ 2.09	1.04 $\pm$ 2.39	0.149
60 min	0.93 $\pm$ 2.19	0.46 $\pm$ 1.75	0.70 $\pm$ 1.98	0.385
120 min	1.37 $\pm$ 0.43	0.0 $\pm$ 0.0	0.21 $\pm$ 0.98	0.104
240 min	1.37 $\pm$ 0.43	0.0 $\pm$ 0.0	0.21 $\pm$ 0.98	0.104
24 hours	1.18 $\pm$ 0.29	0.0 $\pm$ 0.0	0.14 $\pm$ 0.84	0.206

Chi-Square test

Table 3: Frequency distribution of medication status in two groups

Group		Persica		Doxepin		P-value
		Number	percentage	Number	percentage	
Taste	Appropriae	12	42.9	26	92.9	0.000
	Inappropriate	16	57.1	2	7.1	
Level of drowsiness	At all	27	96.4	1	3.6	0.000
	Low	0	0	13	49.4	
	High	1	3.6	14	50	

Chi-Square test

Figures

Figure 1

The mean of pain score in patients with mucositis in the two groups

Figure 2

The mean of burning score in patients with mucositis in the two groups

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