JOURNAL OF CLINICAL AN DIAGNOSTIC RESEARCH

How to cite this article:
SHABANLOEI R , AHMADI F, VAEZ J, ANSARIN K , HAJIZADEH E, JAVADZADEH Y , et al;. ALLOPORINOL, CHAMOMILE AND NORMAL SALINE MOUTHWASHES FOR THE PREVENTION OF CHEMOTHERAPY-INDUCED STOMATITIS.Journal of Clinical and Diagnostic Research [serial online] 2009 June [cited: 2009 June 1]; 3:1537-1542.

Available from
http://www.jcdr.net/back_issues.asp?issn=0973-709x&year=2009&month=June &volume=3&issue=3&page=1537-1542&id=397

ORIGINAL ARTICLE

Alloporinol, Chamomile and Normal Saline Mouthwashes for the Prevention of Chemotherapy-Induced Stomatitis

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ABSTRACT

Background: Stomatitis is a common side effect in patients receiving chemotherapy. It alters survival because of the risk of infection and has a significant impact on the quality of life, causing treatment delays, nutritional deficiencies and increasing the cost of care. The aim of this study was to determine and compare the efficacy of Alloporinol, Chamomile and normal saline mouthwashes in the prevention of chemotherapy-induced Stomatitis.

Methods: A randomized, double-blind clinical trial was conducted on 83 patients receiving chemotherapy. ANOVA, χ^2, Kaplan Meyer and T-test have been used for analyzing the data.

Results:Significant differences were found between Alloporinol, Chamomile and normal saline groups in the scores of the severity of Stomatitis (P=0.017), Stomatitis pain (P=0.027) and in the persistence of Stomatitis. No significant differences were noted among the mean Stomatitis (P=0.59), Stomatitis pain (0.071) and the severity scores of the Alloporinol and Chamomile groups.

Conclusions:These findings indicate the equal efficacy of Alloporinol and Chamomile in the prevention of chemotherapy-induced Stomatitis as compared to the normal saline control group. Considering the cost and easy accessibility of Chamomile and its potential therapeutic applicability in the reduction of the severity of chemotherapy-induced Stomatitis, it has been implied for the prevention of the same.

Key Words: Chemotherapy, Stomatitis, Mouthwash, Chamomile, Alloporinol

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Background

Stomatitis or oral Mucositis is a significant and often debilitating, dose-limiting, and costly side effect in patients treated with cytostatic drugs or radiation therapy [1]. It has been estimated to occur in10% of

patients who receive adjuvant chemotherapy, 40% of patients who receive induction chemotherapy, 80% of patients undergoing stem cell transplant and 90% to 100% of patients undergoing head and neck radiation therapy [2]. It occurs in approximately 52–80% of

children who receive cancer treatment [3]. The untoward side effects and complications of cancer drugs include Stomatitis, delay in cure, the decreasing dose of chemotherapy drugs, severe disturbing pain, nutritional deficiencies, systematic infection, and the increased duration of illness and mortality. Stomatitis carries a higher potential of risk to patients receiving stem cell transplantation (SCT) and increases their mortality up to 100 days post-transplant [4]. In about 35% of those patients that have Stomatitis type 3 or 4, the next period of their chemotherapy is postponed, in about 60% patients, the dose of drugs are decreased and in about 35% of the patients, the consumption of chemotherapy drugs are stopped [5],[6].

Oral Mucositis is considered as a devastating side effect of chemotherapy for several reasons. Patients with Oral Mucositis may have symptoms like painful ingestion leading to nutrition deficiency, dehydration, bacterial and fungal infections, and disturbed mood and sleep [7]. The mucosal pain is the most distressing symptom of the mouth. Mucositis causes nutritional deficiencies, dehydration and severe indigestion [7],[8]. Ulceration of the oral mucosa is caused due to the damage insulted by chemotherapy or radiotherapy on the basal epithelial cells of the mucosa, which decreases the replacement of these cells by new cells. Deprived of new cell replacements, the mucosa becomes narrow, atrophied and ulcerated [5],[9],[10],[11],[12],[13],[14].

Commercially available mouthwashes commonly contain high levels of alcohol ranging from 3 to 50 percent. This may produce a burning sensation in the oral cavity mucosa or may cause intoxication if swallowed or used excessively. For children, even small doses of these rinses may potentially be lethal [15]. It is believed that Chamomile has anti-inflammatory, wound healing, bacteriostatic, antimicrobial and antiseptic activities which annihilate the bad smell in the mouth. [16]. Some studies have suggested that Chamomile essence called α Bisabolol has a strong activity against gram positive and negative bacteria in addition to its anti-inflammatory characteristics [17].Therefore in this study, we investigated the effect of Alloporinol and Chamomile mouthwashes singly and in combination in the prevention of Oral Mucositis in patients undergoing chemotherapy.

Methods

Preparation of mouthwashes**:** Since the essence of the Allopurinol powder is fairly soluble in water, a solution of hydroxyl propyl methyl cellulose was used to prepare a clear and steady solvent of the drug. Based on the achieved solution volume, a little Allopurinol powder was added to it in order to make up the product to 5mg/ml viscosity of the drug. To maintain its physical and chemical stability and to protect it from the growth of micro–organisms,, a mixture of protectors were added to the product.

To prepare Chamomile mouthwashes, the flowers of the plant were used. After grinding and weighing, the flowers in put closed pots and boiling distilled water was added to it in two stages in order to make up the considered volume (8gr in 50^{cc}). The solution was filtered, bottled and sealed. Also, normal saline serum was used as a mouthwash.

Informed consent was obtained from all volunteered subjects. The subjects were selected from patients of the Shahid Ghazi Oncology Services, who were undergoing chemotherapy for various malignancies. The subjects were selected randomly, based on their ID code and by choosing from the box, and were divided into three groups ; received Alloporinol (group I), Chamomile (group II) or normal saline (group III) as gargles of mouthwash daily

for 16 days - four times a day- after starting chemotherapy [Table/Fig 1]

The severity of Stomatitis and Mucositis was evaluated and graded on the basis of the WHO Stomatitis intensity grading system (grade 0 indicating no Stomatitis and 4 representing the most severe form of Stomatitis with ulceration and bleeding), and the intensity of pain resulting from Stomatitis was recorded according to self-reporting tools (zero shows no pain and 10 shows the most intense pain).

This study was designed and conducted by a double-blind system, so that both co-workers,who followed up the patients and the patients didn't know the type of mouthwashes used.

Results

Demographical, clinical and laboratory findings of all subjects and groups are summarized in [Table/Fig 1].

[Table/Fig 1] Comparison of demographic, clinical and laboratory factors of the objects

Factor Group	Allopurinol	Chamomile	Normal saline	P_{value}
Sex (M/F)	16/12	19/9	12/15	0.22+
Age (years) mean±SD	32.46±13.36	33.71±14.03	34.04±13.96	0.90*
Body surface(m^2) mean±SD	1.65±0.15	1.65±0.12	1.66±0.13	0.89*
Diagnosis(month) mean±SD	3.43±1.56	3.57±1.57	3.71±1.38	0.78*
Decayed tooth	1.14±1.65	1.04±1.53	0.54±1.07	0.21*
Smoking history	1.86±3.53	1.07±3.15	0.21±0.80	0.41*
Hb mean±SD	9.08 ±1.86	10.05±1.90	10.51±5.17	0.73*
WBC mean±SD	34346.8±3708.4	3768.2± 3586.7	5575.4±5601.1	0.31*
Neut mean±SD	48.65±19.08	45.16±18.86	49.67±25.77	0.72*
Lym mean±SD	35.61±18.60	38.12±18.10	32.23 ±23.29	0.57*
Plt mean±SD	166050.0±16544 3.4	148996.4±14494 7.5	193576.9±13318 2.0	0.54*

Abbreviation: Hb, hemoglobin. WBC, white blood cell. Neut, neutrophil. Lym, lymphocyte. Plt, platelet

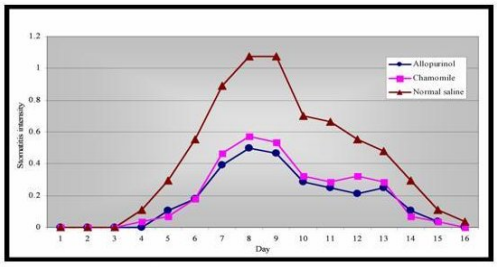
+ χ^2 test * ANOVA test

There was no significant difference in the Fisher Exact test between the education levels (P= 0.69) or the type of the cancer (P=0.68) in the three types of mouthwash used.

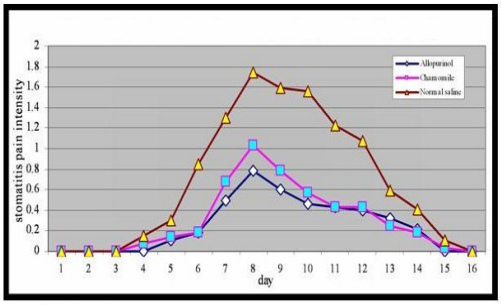
The functions of the bone marrow and the immune system were found to affect the intensity of the stomatitis directly and indirectly. So the results of patients were compared between the three groups [Table/Fig 1]. Considering the clinical mechanism of mucositis and for more precise investigation, the average Stomatitis intensity and its pain were investigated in four phases during four days [Table/Fig 2],[Table/Fig 3],[Table/Fig 4].

(Table/Fig 2) Investigation of three groups' Stomatitis and pain intensity

Group Result	Stomatitis		Pain	
	Mean ± SD	Kruskal-Wallis	Mean ± SD	Kruskal-Wallis
Allopurinol	0.17±0.23	P=0.017	0.25±0.37	P=0.027
Chamomile	0.20±0.23		0.30±0.44	
Normal saline	0.43±0.41		0.68±0.68	



(Table/Fig 3) Ivestigation of thre 'groups' stomatitis



(Table/Fig 4) Invention of thre 'groups 'stomatitis pain intensity

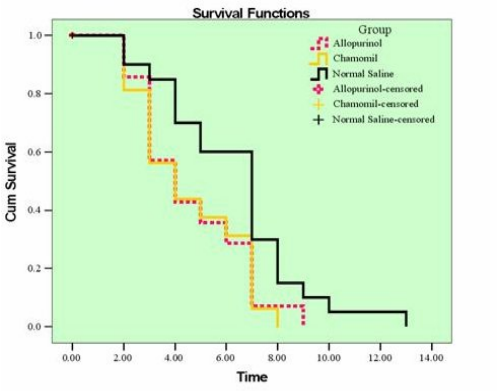
No significant difference was found between the Alloporinol and the Chamomile groups in the variability of the Stomatitis and total intensity during the first to the fourth time period. However, the normal saline group showed a significant difference with regard to the Stomatitis intensity variables when compared to the Alloporinol and the Chamomile groups. The Stomatitis pain intensity significantly differed in the Alloporinol group from that of the normal saline group, during the second and third time periods and in the Chamomile group during the third time period [Table/Fig 5].

(Table/Fig 5) Comparison of Stomatitis and pain intensity during four time periods

Group	Variable	Stomatitis Intensity*				
Mean	*Comparative*	Total	Phase I	Phase II	Phase III	Phase IV
Allopurinol	Chamomile	0.59	0.32	0.89	0.61	0.80
Allopurinol	Normal saline	0.00	0.72	0.00	0.01	0.17
Chamomile	Normal saline	0.01	0.30	0.01	0.04	0.18
Mean	*Comparative*	*Stomatitis Pain Intensity**				
Allopurinol	Chamomile	0.71	0.32	0.83	0.80	0.68
Allopurinol	Normal saline	0.00	0.15	0.01	0.02	0.30
Chamomile	Normal saline	0.02	0.54	0.05	0.03	0.25

* U Mann-Whitney test

The Kaplan-Meier survival analysis revealed a significant difference with regard to the total disease time between the three groups. (P=0.04). Comparison of Alloporinol and Chamomile groups failed to show any significant difference with regard to Stomatitis survival (P = 0.82). However, the normal saline group had a significantly different survival (P=0.00) [Table/Fig 6]



(Table/Fig 6) Stomatitis survival test in three groups

Discussion

Mucositis still remains a persistent problem in many oncology centers. Limited progress has been made in the treatment and prevention of this complication caused by chemotherapy. Stomatitis, a well-known form of Mucositis, is one of the important cases of nursing intervention in the hospitalized cancer patients [18],[19]. Though Stomatitis is believed to be an inflammatory condition, most studies have already concentrated on antimicrobial mouthwashes as a remedy for it. Therefore, this study was performed to compare the effectiveness of Alloporinol and Chamomile on Stomatitis.

Many factors may affect the appearance of the time period of the Stomatitis and its intensity directly or indirectly. So these agendas were compared between groups.

Jakel has reported that the effect of the chemotherapy on bone marrow causes anaemia, which directly or secondarily acts as a factor for chronic inflammation and releases cytokines such as tumour necrosis factor, gamma-interferon, and interleukin-1 [21]. As interleukin-1 and tumour necrosis factor have a recognized role in the production of Stomatitis, investigating the rate of haemoglobin is necessary in this research. ANOVA test done on the average haemoglobin levels of those three groups did not show significant variations. The beginning of the healing phase of oral Mucositis is marked by an increase in the white blood cell count, especially the neutrophil count and by a decrease in bacterial colonies [22].

The result of this investigation shows that both Alloporinol and Chamomile mouthwashes could decrease the intensity of the Stomatitis caused by chemotherapy and its pain in comparison to the normal saline group.

Clark and Slevin reported that six patients who were afflicted with colorectal cancer and were under treatment with 5-fluorouracil by injecting the bolus drug, developed Stomatitis due to 5-fluorouracil. They were advised to gargle with a 15 to 20^{cc} Alloporinol mouthwash solution (1 mg in 1 ml water) at the time of chemotherapy and all of them showed considerable improvement after this treatment [23].

In 1990, Loprinzi in his studies investigated the effect of the Alloporinol mouthwash indefinitely to prevent Stomatitis caused by chemotherapy. In this research, 77 patients afflicted with colorectal cancer that were receiving 5-fluorouracil in the form of bolus or

leucvorin, were put in one of the Alloporinol and placebo groups according to their age. They were first trained to wet their lips with the solution and to wash their mouth with its 20^{cc} solution for 30 seconds at the time of receiving the chemotherapy and 1, 2 or 3 hours thereafter. The Alloporinol solution was not effective [24]. However, these findings cannot be clinically valid as inflammatory cytokines increase 4 or 7 days after chemotherapy. So, any interference should be made within the first two weeks of chemotherapy in order to reduce the risk of Stomatitis. In 2002, Hanawa investigated the preventive effect of the Alloporinol spray which was administered 3 or 5 times a day in post-chemotherapy Stomatitis and showed that their patients who underwent this regimen had a lower rate of Stomatitis [25].

Conclusions

The results of this study show that Alloporinol and Chamomile mouthwashes are equally effective in reducing post-chemotherapy Stomatitis. Hence, the Chamomile mouthwash can be safely and effectively administered for patients on chemotherapy for its easy availability and cost-effectiveness.

Acknowledgements

The authors would like to thank Marandi R and Eftekhrian M, for the assessment of the patient's mouth during the 16 days and in helping to coordinate the project. Special thanks to Atabak Asvadi Kermani for his help in the final edition of this article.

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