



Clinical Research

Protective effect of *Yashtimadhu* (*Glycyrrhiza glabra*) against side effects of radiation/chemotherapy in head and neck malignancies

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Abstract

One of the very common side effects of Radiation/Chemotherapy especially of the head and neck malignancies is mucositis. Cancer therapy or the cancer itself may cause changes in the body chemistry that results in loss of appetite, pain, nausea, vomiting, diarrhea and very common mucositis which makes eating difficult. Loss of appetite is followed by an undesirable loss of weight due to insufficient amount of calories every day which can lead to loss of muscle mass and strength and other complications by causing interruptions of medical therapy, impeding effective cancer therapy. Mucositis cause decreased immunity and quality of life as well as poor tolerance to surgery and altered efficacy of Chemotherapy and Radiotherapy. The present study is designed with the objective to minimize the radiation induced mucositis, skin reaction, xerostomia, change in voice etc. with an Ayurvedic preparation *Yashtimadhu Ghrita* (processed ghee). Total 75 patients were randomly divided into four groups and drugs were administered: Group A with local application of *Yashtimadhu* powder and honey in the oral cavity for few minutes prior to radiotherapy along with oral intake of *Yashtimadhu Ghrita*; Group B with only local application of the *Yashtimadhu* powder and honey in the oral cavity; Group C patients administered with only local application of honey in the oral cavity; Group D on conventional modern medication controlled group. All these patients under four groups had received Radiotherapy and Chemotherapy for maximum duration of 7 weeks. Mucositis and Skin reactions were observed in 100% of patients with varying degree. The intensity of Radiation and Chemotherapy induced mucositis was reduced to a great extent by the trial drug. *Yashtimadhu* (*Glycyrrhiza glabra*) can be used effectively in prevention and treatment of oral mucositis post radiation and chemotherapy in patients of cancer, especially of the head and neck region. It proves beneficial in two ways: (i) there were no interruptions in the treatment, and (ii) food intake was not severely affected leading to maintenance of nutritional status of the patients.

Key words: Head and neck cancer, oral mucositis, radio-chemotherapy, *Yashtimadhu ghrita*

Introduction

Oral cancer is one of the most common cancers in the world, commonest in India, Bangladesh, Srilanka and Pakistan. In India, head and neck carcinoma^[1] (HNCA) account for 30-40% cancers at all sites, out of which 9.4% are oral cancers. It is the sixth common cause of death in males and seventh in females. In North-east India, incidence of tobacco related oral cancers is about 33%. The morbidity and mortality associated with

this disease is a cause of major concern in this region. Many factors implicated for its preference are consumption of tobacco in its various forms, alcohol, smoking habits, poor oral hygiene, lack of awareness, and lack of proper nutrition. No complication of cancer treatment^[2] is more acutely distressing than stomatitis. The oral cavity, normally a delicately balanced and exquisitely sensitive portal, can become a site of extreme discomfort. Stomatitis, or oral mucositis, is defined as the inflammation of the oral mucous membranes. Such inflammation affects one's sense of taste and smell, as well as nutrition and hydration, and may well reduce the palatability of oral medications. Oral Mucositis^[3] occurs in 15-40% of patients receiving standard chemotherapy and 100% of patients receiving radiation therapy for head and neck cancer are afflicted with oral mucositis of varying

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degree. Currently, the world wide population with mucositis is estimated at 400,000 to 600,000 receiving chemotherapy or radiation. Ionizing radiation^[4] causes various changes in normal tissues, depending on closely interrelated factors of total dose, fractionation schedule (daily dose and time), and Volume treated.

In Ayurvedic classics like *Charaka samhita*^[5] and *Sushruta samhita*^[6] cancer is described as *Arbuda* (major neoplasm) or *Granthi* (minor neoplasm) and *Tridoshaja/Sannipataja* varieties of as the malignant stage of neoplasms or abnormal growths have been described. *Ayurveda* can be helpful in the management of cancer in many ways, as prophylactic, palliative, curative and, supportive and undoubtedly it helps to improve the quality of life (QOL),^[7] as an adjuvant therapy along with chemotherapy or radiotherapy and post surgery care, to minimize the side effects of these therapies. Although the adverse effects of radiotherapy and chemotherapy cannot be totally avoided, there are ways to minimize the side effects of these treatment procedures. Therefore, an attempt has been made to minimize the radiation induced mucositis, skin reaction, xerostomia, change in voice etc with an Ayurvedic *Ghritha* preparation i. e. *Yashtimadhu Ghritha*.^[8] Also, we have tried to assess the efficacy of the prepared drug in the healing or protection of the above said side effects.

Materials and Methods

Selection of patients

Inclusion criteria

Patients between 30-60 years attending the Radiotherapy Department of Guru Govind Singh Hospital, Meghji Pethraj Shah Medical College, Jamnagar with histopathologically proven head and neck malignancies, and who had not initially been treated by Radiotherapy, and were selected for administering Radiation Volume between 100cm² to 170cm² subject to hemoglobin concentration $\geq 9\%$ and Serum protein within normal limits, were included in the study.

Exclusion criteria

Those patients who were on palliative course of treatment, who had taken Radiotherapy earlier, were below 30 years and above 60 years of age with history of Hypertension, Cardiac Ailments, Diabetes and those allergic to Platins', were excluded from the study.

Drug collection and authentication

Yashtimadhu roots were collected from a dealer in Ahmadabad. The pharmacognostical study of the trial drug i. e. *Yashtimadhu* was carried out in the Pharmacognosy laboratory, Institute for Post Graduate Teaching and Research in Ayurveda, Jamnagar. The root of the raw drug and its powder was used for microscopic assessment and authentication.

Pharmacognostic study

- Organoleptic Study: The root powder was evaluated for organoleptic characters like colour, odour and taste
- Liquorice Root: A pale, yellowish-brown powder with a faint, characteristic odour and a sweet taste.
- Part used: Rhizome (underground stem), Root

Description

Licorice is a perennial herb that grows up to three feet tall and

has a woody, branching, brown rhizome (underground stem) that is yellow inside. Compound leaves are composed of three to seven pairs of oblong leaflets and while purplish flower bloom in terminal spikes. Fruits are smooth and reddish brown pods are seen.

Method of preparation of *Yashtimadhu Ghritha*

Yashtimadhu Ghritha was prepared according to *Sneha Kalpana Vidhi*. *Yashtimadhu choorna* (powder) (1 part) was taken and made into a paste form by mixing it with sufficient quantity of water and keeping it aside. Cow's ghee (4 parts) was heated over a big vessel till the water content was evaporated. *Yashtimadhu kalka* (paste) was made into a small bolus and poured into the ghee and fried for few minutes. 16 parts of water was then added into the mixture for preparation of the *Yashtimadhu ghritha* by *sneha paka* procedure. The whole content was heated for three days consecutively to evaporate the whole water content and leave behind only the ghee (*ghritha*) portion, which was then filtered by a thin cotton cloth and the final *Yashtimadhu Ghritha* was obtained.

Total 75 patients were registered and randomly divided into four groups

Group A- Patients' administered with local application of the *Yashtimadhu* powder and honey, along with oral intake of *Yashtimadhu ghritha*, 10 ml twice daily. In this group, total 26 patients were registered and 18 completed the full course of treatment.

Group B- Patients' administered with only local application of the *Yashtimadhu* powder and honey. In this group, 17 patients were registered and 12 completed the treatment.

Group C- Patients' administered with only topical application of honey. In this group, out of 12 patients registered, 9 completed the treatment.

Group D- Control group of patients' only on conventional modern medication, where 20 patients were registered and 13 patients completed the full course of treatment.

All patients under the four groups received modern medication- Radiation/Chemotherapy as per the need.

Criteria of assessment

Patients were assessed on the basis of clinical presentation of side effects of Radiotherapy and Chemotherapy, with their grading system as recommended by *Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC)*^[9] Radiation Morbidity Scoring Scheme [Table 1].

Observation and Results

In Table 2, BT (before treatment) is taken as 2nd week of radiotherapy (RT) and chemotherapy (CT) when the side effects first appear and AT (after treatment) is taken as end of treatment (6th/7th week).

Most common age in all 4 groups was 41 to 60 years (80.07%, 64.70%, 83.33%, 85% in Group A, B, C and D respectively) followed by 31 to 40 years (19.20%, 35.29%, 16.66% and 15% in group A, B, C, and D respectively). Maximum number of patients (85.33%) was male whereas 14.66% were female. Maximum number of patients (74.66%) smoked Bidis followed by 22.66% of chewing *Mawa*, 1.33% and 6.66% smoking cigarettes and applying Bujjar on the oral cavity, respectively. All

Table 1: Grading of adverse effects caused by Radiation/Chemotherapy in the patients participating in the study

Organ/tissue	Grade				
	0	I	II	III	IV
Mucous membrane (Mucositis)	None	Soreness with erythema	Patchy fibrinous mucositis	Confluent fibrinous mucositis	Ulceration
Skin	None	Erythema/Pigmentation	Dry desquamation vesiculation pruritis	Moist desquamation ulceration	Exfoliative dermatitis necrosis
Salivary glands (xerostomia)	None	Slight dryness of mouth/good response on stimulation	Moderate dryness of mouth/poor response on stimulation	Complete dryness of mouth/no response on stimulation	Fibrosis
Larynx (change in voice)	None	Hoarseness/Slight arytenoids edema	Moderate arytenoids edema	Severe edema	Necrosis

Table 2: Comparison of side effects between the study groups (A, B and C) and control group D before and post the radiation and chemotherapy

Groups	Reactions	Before treatment		After treatment	
		χ^2	P	χ^2	P
A	Mucositis	6.71	<0.001	7.04	<0.001
	Skin reactions	0.34	>0.1	0.34	>0.1
	Xerostomia	0.014	>0.1	4.39	>0.1
	Change in Voice	0.014	>0.1	14.39	<0.001
B	Mucositis	3.20	>0.1	8.98	<0.001
	Skin reactions	6.82	<0.001	0.46	>0.1
	Xerostomia	0.12	>0.1	2.30	>0.1
	Change in voice	11.58	<0.001	14.42	<0.001
C	Mucositis	1.50	>0.1	1.22	>0.1
	Skin reactions	0.02	>0.1	2.58	>0.1
	Xerostomia	1.22	>0.1	0.86	>0.1
	Change in voice	4.03	>0.1	2.26	>0.1

the patients (100%) were irradiated on the right and left lateral face and neck, the surface markings were from above tragus to upper border of clavicles below. All the patients (100%) had radiation induced Mucositis and Skin Reaction of varying degree followed by 98% Xerostomia and 88% Change in Voice as the side effects of both Radiation and Chemotherapy. The average field size of group a patients is 12.88 × 10.55 cms whereas it is more or less equivalent in other groups. Histopathologically maximum number (99%) of the patients had squamous cell carcinoma and only one patient (1%) had muco epidermoid carcinoma. Maximum (38.46% and 41.66%) interruptions, two patients had 10 days of interruptions in group C and 1 patient in control group D. In study group a it was least (16.66%) interruption in comparison to all other groups.

Discussion

Sushruta's description of *Arbuda* covers the neoplasms: benign and malignant, as available in recent medical literature. Though detailed principle of management is narrated in ancient classics, practically it is the modern approached of surgery, chemotherapy and radiotherapy that are modalities administered to the patients. Maximum patients were 50 years of age and above, which is considered as *Praudhavastha* in *Ayurveda*, i. e. late adult hood;

and, cancer in contemporary science is considered as an old age disease. Gender predilection was towards male dominancy (85.33%) in head and neck cancer prevalence rate in our study. There was statistically a marked reduction in the appearance and severity of mucositis in group A when compared to group D in the 2nd week of radiotherapy, which is highly significant ($P < 0.001$). The same significance is seen in the last week of radiotherapy and chemotherapy i. e. grade III mucositis which was comparatively less in group A than in group D. In group B, the results on mucositis as compared to group D are not significant in the 2nd week of radiation therapy ($P > 0.1$); however, in the 7th week the results are statistically highly significant i. e. $P < 0.001$. In group C, the statistical analysis reveals that in both the 2nd and 7th week of treatment schedule, the results on mucositis in comparison to group D are insignificant ($P > 0.1$).

The trial drug of group A *Yashtimadhu ghrita* orally and *Yashtimadhu* powder with honey locally had insignificant result ($P > 0.1$) in skin reactions in both initial stage and in final week of the treatment when compared to the control group D. In group B the trial drug had highly significant results ($P < 0.001$) in both 2nd week and 7th week of radiotherapy and chemotherapy. The skin reactions were of low grade in comparison to skin reaction in comparison to patients of control group D. These changes that occurred with the treatment may be due to the *Varnya* properties (which bestows good complexion) of *Yashtimadhu* powder. Xerostomia symptoms were persistent in all the groups and *Yashtimadhu ghrita* has shown no effect on this particular side effect. The intensity of change in voice was gradually increasing as the treatment progressed. In group A the effect on change in voice was statistically insignificant ($P > 0.1$) in 2nd as well as in 7th week but the result was surprisingly highly significant in study group B in 2nd and 7th week ($P < 0.001$) while in group C the therapy had insignificant results on both initial and final week of therapy ($P > 0.1$). The change in voice has a statistically significant result in group B which may be due the *Swarya* (promoting good voice) property of *Yashtimadhu* powder. The results are substantially good in comparison to control group D.

Though the hemoglobin percentage (Hb%) did not rise in group A, it was maintained within normal limits which is quite appreciable in the pretext of the disease condition and the invasive treatments of radiotherapy and chemotherapy. It also cannot be ruled out that the trial formulation was ineffective in increasing Hb% level since duration of treatment was for 7 weeks which is not sufficient enough to expect any significant rise in hemoglobin level. In study group B and C, the Hb% and total leukocyte levels (TLC) did not show any

significance statistically but in both the groups it's within normal limits the levels were maintained within normal limits. Similarly renal function was also within normal limits in all the study groups (A, B and C) revealing that *Yashtimadhu* is not nephrotoxic since the chemotherapeutic drug administered in these patients is Cisplatin and the incidence of renal insufficiency is about 5% with adequate hydration measures and 25% to 45% without hydration measures.

Probable mode of action

Yashtimadhu ghrita showed encouraging results in minimizing the side effects of radiation and chemotherapy. *Yashtimadhu*^[10] has *madhura rasa*, *sheeta virya*, *madhura vipaka*. It is *vata-pitta shamaka*. Moreover, studies conducted on modern scientific parameters have proved the healing, anti-ulcer,^[11] anti-inflammatory and skin regeneration activity of *Yashtimadhu*. Sodium, glycyrrhizate possessed anti ulcer activity and stimulation of regeneration of skin. Honey^[12] (*madhu*) has properties such as *madhura rasa* and *kashaya anu rasa*. It is heavy (*guru guna*), dry (*ruksha*) and cold (*sheeta*). It aggravates *vata*, scrapes *kapha* and normalizes *pitta* and *rakta*. It promotes healing process.

Conclusion

First and foremost, the intensity of radiation and chemotherapy induced mucositis was reduced to a great extent by *Yashtimadhu ghrita*, which proved beneficial in two ways: (i) there were no interruptions in the treatment, and (ii) food intake was not severely affected leading to maintenance of nutritional status of the patients. Higher prevalence of male sex is evident, probably due to the addiction to smoking of bidis and tobacco chewing which contribute as carcinogens, and thus increase the risk of such malignancies in males in comparison to the opposite gender. The side effects were more visible in *Pitta* dominant *prakriti* (body constitution), which can be understood in the

line of *gunas* (properties) (*Ushna and Tikshna*) of both the invasive treatments, i. e. RT and CT since radiation may be compared to *Agni* and chemotherapy to *Visha aushadhi*. The hematological levels were maintained within normal limits' and the drug had no adverse effect on kidneys, which helped in timely administration of chemotherapy thereby preventing any delay in the scheduled doses. Xerostomia symptoms were persistent and the trial drug caused no improvement on this particular side effect. There were no side effects of the trial drug in all the study groups and it was well tolerated by the patients throughout the study.

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हिन्दी सारांश

शिरः एवं मन्या अर्बुद में रेडियेशन/ किमोथेरेपि के दुष्परिणामों में यष्टिमधु का संरक्षात्मक प्रभाव

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मुखपाक(म्युकोसायटिस) शिरः एवं मन्या अर्बुद में दिये जाने वाले रेडियेशन/किमोथेरेपि के दुष्परिणामों में से एक सामान्य लक्षण है। मुखपाक के कारण व्याधिक्रमत्व एवं जीवनमान विपरीत तरह से प्रभावित होता है। प्रस्तुत अध्ययन रेडियेशन/किमोथेरेपि के दुष्परिणाम जैसे मुखपाक, त्वक्विकार, लालास्राव हास, स्वरसाद आदि में आयुर्वेदीय औषधि यष्टिमधु घृत के प्रभाव का मूल्यांकन किया गया। प्रथम समूह में रेडियोथेरापि से पहले यष्टिमधु चूर्ण एवं मधु का मुख की श्लैष्मत्वचा पर लेप किया गया और यष्टिमधु घृत का सेवन कराया गया। द्वितीय समूह में केवल यष्टिमधु चूर्ण एवं मधु का लेप किया गया। तृतीय समूह में केवल मधु का लेप किया गया। चतुर्थ नियंत्रित समूह में केवल आधुनिक रेडियोथेरेपि/किमोथेरेपि अधिकतम सात सप्ताह तक दी गयी। आधुनिक चिकित्सा प्रथम तीनों समूहों में भी दी गई थी। परिणामों के विश्लेषणों के पश्चात यह पाया गया कि यष्टिमधु घृत एवं चूर्ण रेडियेशन एवं किमोथेरेपि से उत्पन्न मुखपाक की तीव्रता कम करने में सक्षम है।