Phase-III Randomized trial comparing topical application of natural honey in the management of radiation mucositis among patient undergoing radical radiotherapy for nasopharyngeal cancer.

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Abstract:

Introduction: Radiation mucositis is a very common acute morbidity suffered by almost all patients undergoing radiotherapy to the head and neck region. Materials and Methods: This is a prospective double blind randomized control trial comparing topical application of natural honey in mucositis induced by chemo-radiotherapy in nasopharyngeal cancer. One hundred twenty patients were treated with chemo-radiotherapy using cisplatinum. Radiotherapy consists of 70Gy in 35 fractions over 7 weeks period along with 30mg parenteral weekly cisplatinum was administered. Sixty (60) patients were subjected to topical application of honey before and after each fractions of radiotherapy. The mucositis, dysphagia and dry mouth were assessed using RTOG grading system. Weekly body weight monitoring, the EORTC QLQ-H&N35 and general EORTC QLQ-C30 questionnaire were recorded before and after radiotherapy. Results: There were 82 males and 38 female with a median age of 48 years (10-81years) in this study. The compliance to honey and placebo application was poor in our patient population with only 49-patients (40.8%) accepted complete course; 21 (17.5%)-incomplete and remaining refused application including 6-patients developed adverse effects in the form of burning mucosal pain. The concurrent chemotherapy was accepted in 51(42.5%) patients, incomplete in 67(55.8%) patients and not received in 2 (1.6%) patients. The quality of life in Head & Neck specific scale changed from 42 to 54 points in study arm and 43 to 54 points in control arm. The grade4 mucositis appeared to be less in honey treated arm compared to controls whoever other grades of mucositis or weight changes was equivocal in both arms Conclusions: Due to non-compliance of topical application of study agents, there was no significant difference in mucositis, body weight, dysphagia grade or dry mouth in study and control group of patients. Proper selection of honey, method of application of honey with mucosal adhesion properties might reveal improvement of mucositis in future research.

Key words: Radiation mucositis, chemotherapy, honey, treatment, response, body weight

Introduction

Radiation induced mucositis is a well known accompaniment of radiation treatment to the head and neck area. Mucositis leads to oral ulceration causing pain and dysphagia to discontinuation of treatment or gap during radiotherapy. A gap during the course of radiotherapy leads to loss of local control in many cancers including head and neck cancers[1]. The incidence of radiation mucositis varies due to field size, co-morbid mucosal condition and systemic disease, orodental infection. Modern radiotherapy techniques like hyperfractionation, accelerated fractionation, CHART has increased the rate of mucositis[2-3]. Currently administration of chemotherapy as radiosensitizer (concurrent chemotherapy) has shown to improve survival in head and neck cancer compared to conventional fractionated radiotherapy[4-5]. The occurrence of mucositis is a dose limiting toxicity in the management of head and neck cancers undergoing radiotherapy. Systemic disease like diabetes mellitus and connective tissue diseases and re-irradiation can also increases the rate of mucositis. The severe form of mucositis (NCI CTC grade3 & 4) are symptomatic and affect the health and outcome of cancer in the above region. Currently the pathophysiology of induction of radiation mucositis is changing. The current research has identified multi-step process for radiation mucositis. The process of radiation mucositis goes through 4-defined steps[6]. Therefore no single treatment is effective in radiation mucositis as they do not address all aspects of mucositis. Currently there is no standard of care for the treatment of radiation mucositis[7]. Frequent salt soda solution oral rinse is the most common management of mucositis in many radiotherapy centers. From the plethora of agents being tried in radiation mucositis; amifostine, human placental extract etc has shown some response from the outcome of meta-analysis. Radiotherapy techniques such as oral shielding and IMRT are used to reduce the intensity of mucositis. Honey is a mixture of nectar, aerodigestive tract of the honey bee and part of the honey comb. It has tissue repairing, epithelization, caloric properties. It too reduces inflammation and clear oral pathogens, an earlier study on the role of honey in the management of radiation mucositis has shown to reduce severe mucositis and mucosal pain[8-9]. From the earlier experience on the use of honey in radiation mucositis

we proposed a multicenter randomized trial in the management of radiation mucositis induced by concurrent chemoradiotherapy in the management of nasopharyngeal cancer.

Materials and Method

This is a prospective multi-center double blind randomized trial comparing the difference of radiation mucositis between honey and placebo group of patients with nasopharyngeal cancers on concurrent chemoirradiation. The patients were recruited from Hspital Universiti Sains Malaysia, Hospital Kuala Lumpur, and Sarawak General Hospital. The case selection includes locally advanced nasopharyngeal cancer patients with histological proof of cancer, good performance status age between 15-85 years. Patients with unlocalized tumor, patients suffering from connective vascular disease were excluded from the study.

Randomization

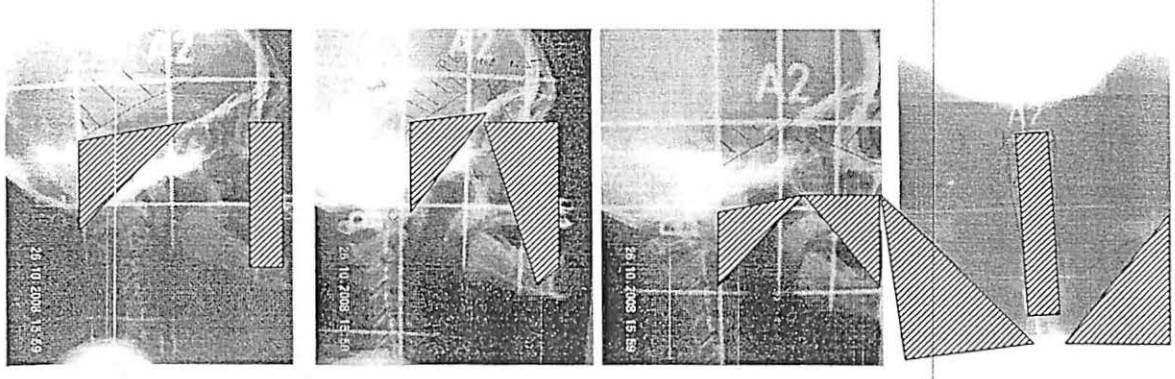
The randomization was controlled centrally at USM. The doctors, researchers and patient did not know the study agent. The research assistant recruits patients. The patients were evaluated using nasoendoscopy, contrast enhanced CT scan of the head and neck, full blood count, liver and kidney chemistry were performed prior to recruitment of patients.

Treatment with research agents

The patients belong to study arm were treated with concurrent chemo-radiotherapy and honey treatment. About 20 ml of the research material was allowed to keep inside mouth and to swish and swallow the whole content 15 minutes before, 15 minutes after and 6 hours after radiotherapy. The treatment continued throughout the course of radiotherapy. The control groups of patients were given along-with similar concurrent chemo-radiotherapy and dose schedule throughout the course of radiotherapy.

Radiotherapy

The administration of radiotherapy consists of three phases. The phase-I consists of the whole primary tumor extent plus safe margin and draining lymphatic regions. The typical field extends from base of the skull until clavicular area that includes the whole extends of mucosa. Usually a 6 MV x-ray was used from a linear accelerator. The spine was excluded from the beam after 44Gy and the final boost was delivered to the primary tumor plus 2 centimeters of safe margin (Fig- 1-a-d). The bulky nodal areas were boosted up to 70Gy. Care was taken to reduce gap during radiotherapy.



Phase-I Phase-II Phase-III Phase-I&II

Fig-1a-d. Serial simulator films of phase-I, phase-II, phase III radiotherapy plan. The lower neck field was used in phase-I & II only. Please note 5HVL lead shields to protect brain, brain stem, orbit, spinal cord and lungs.

Chemotherapy

Cisplatinum single agent chemotherapy d was administered through intravenous route concurrently to a dose of 30 mg in 1 hour infusion once weekly for up to 7 weeks. Parenteral hydration, granisetron and dexamethasone were used for prevention of nausea and vomiting. The chemotherapy was administered on the 1st working day of the week before radiotherapy.

Evaluation of mucositis and body weight

The mucositis was graded using RTOG grading system. The evaluation was done every week and recorded. The dysphagia and skin reaction too was graded as per the RTOG grading system (Fig- 2a-c). The lean body weight was also recorded every week using same weighing machine.

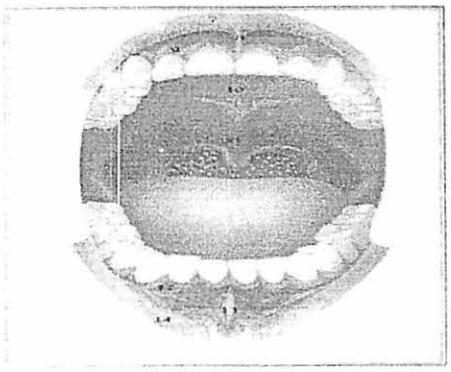


Fig-2a. Schematic diagram of the oral cavity showing 9-sites of the oral cavity required to be evaluated during mucositis assessment.

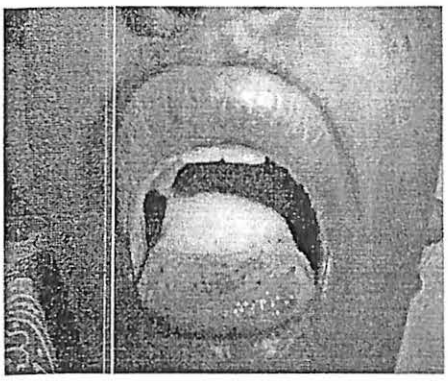


Fig-2b. A case of severe (RTOG grade-III) cancer treatment related mucositis. Please note the confluent mucositis all over the dorsum of tongue. The patient also suffered from severe dysphagia.

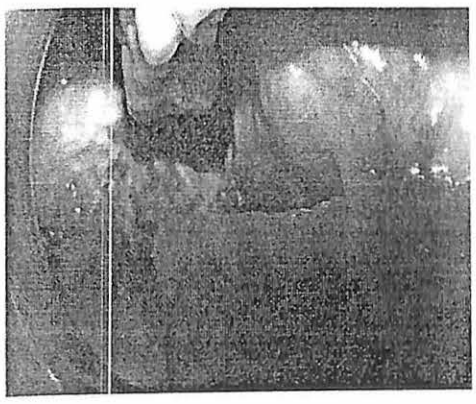


Fig-2c. Close-up picture of the oral mucosa area on the buccal aspect of cheek showing breach in the continuity of the mucosa. Note erythema in addition to ulceration.

Evaluation of quality of life

The quality of life was recorded before and after radiotherapy using EORTC C-30 and Head & Neck C35 questionnaire in Bahasa Malaysia language.

Statistical Analysis

The patient's data were analyzed using SPSS-11 software and multivariate analysis. The results were compared using chi-square test.

Results

One hundred twenty nasopharyngeal cancer patients were recruited from three centers from Malaysia. The median age of the study and control arm of patients was 47 and 50 years in controls and study groups of patients that range from 10-81 years. The race distribution was as follows Malays (30%), Chinese24%, Ibans (23%) and other races in 7.5% of population. There were 40 and 42 males and 20 and 18 females in the control and study groups of patients (Table-1). Study was conducted between January 2005 to July 2007 at Hospital Universiti Sains Malaysia, Hospital Kuala Lumpur, and General Hospital Sarawak at a ratio of 24:16:80 patients. The stage distribution and racial distribution of patients were similar in both groups (Table 1).

Table-1. Patients demography and disease profile

	Control Group	Study Group
Number	60	60
Gender (Male)	40 (33%)	42 (36%)
Gender (Female)	20 (16.5%)	18 (15%)
Age	47(19-71)	50(10-81)
Stage(T1-4)	19/18/14/9	15/16/17/12
HPE type#	4(3%)/23 (19%)/32 (26%)	4(3%)/27(22%)/27(22%)
Race*	18/16/15/11	18/13/13/16
T1	15	19
T2	16	18
T3	17	14
T4	12	9
No	15	12
N1	18	8
N2	19	25
N3	8	15
G1	4	4
G2	23	27
G3	32	27
Poor ODH	10	12
Good ODH	47	42
Died	1	4
Tumor dose	70Gy	70Gy
Fieldsize	205.5cm^2	210.4cm^2

*Malay (30%)/Chinese(24.2%)/Iban (23.3%)/Bidayuh 7.5%,Others (15%);

HPE G1 6%, G2 42%, G3 49%

Concurrent chemoradiotherapy.

Our patients were offered 30 mg of cisplatinum parenterally on the 1st day of the radiotherapy. Out of 120 patients 51(42%) received complete course of single agent cisplatinum chemotherapy whereas incomplete cycles was delivered to 67 patients (57%) where the reason of discontinuation was incomplete. (Table-2)

Compliance of honey treatment: Out of total 120 patients 49 patients actually received complete course of honey/placebo agents. 44 (36%) refused research agent treatment due to poor taste of the research material. Incomplete treatment was offered to 21 (17%) patients and adverse effect was seen among 6-patients mainly due to severe burning sensation in oral mucosa. (Table-2)

Table-2. Compliance to treatment

	Control	Honey
Number recruited	120(100%)	120
Completely received	51(42.5%)	49 (40.8%)
Incomplete cycles*/treatment	67(55.8%)	21 (17.5%)
Insufficient reason	02(01.6%)	
Refused treatment mid-RT		44 (36.7%)
Adverse effect (burning pain)		06 (5%)

*Incomplete chemotherapy :2-weeks- 9, 3-weeks-11, 4 weeks-8, 5 weeks-13, and 6 weeks 33 patients

Mucositis prevalence

Mucositis was evaluated routinely every week. The grade 1-4 mucositis were similar in control and study arm of patients. The grade 3/4 mucositis was marginally lower in honey treatment compared to placebo group of patients (Table 3). Similarly grade 3/4 dysphagia was also lower among honey treated group of patients (Table 4). The rate of xerostomia was almost similar (Table-5).

Table-3. Mucositis Pattern

	Honey Treated Arm					Control Arm				
Weeks	0	1	2	3	4	0	1	2	3	4
1	83.2	16.9				86.7	13.3			
2	39	54.2	6.8			53.4	41.4	5.2		
3	22.6	52.8	20.8	3.8		26	60	14		
4	16.3	51	24.5	8.2		14	60.5	25.6		
5	13.6	50	27.3	9.11		7.7	51.3	30.8	10.3	
6	11.4	42.9	31.4	11.4	2.9	8.1	48.6	29.7	8.1	5.4
7	6.9	44.8	24.1	17.2	6.9	9.1	45.5	21.2	18.2	6.1
8	7.7	46.2	30.8	15.4		12.5	31.3	43.8	12.5	

Table-4. Pattern of Dysphagia

	Honey Treated Arm					Control Arm				
Weeks	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
1	83.1	18.6				90	13.3			
2	39	44.1	6.8			53.4	41.1	5.2		
3	22.6	66	9.4	**3.8**		26	60	14		
4	16.3	63.3	18.4	**6.1**		14	60.5	25.6		
5	13.6	59.1	20.5	**13.6**		7.7	51.3	30.8	**10.3**	
6	11.4	27	16.2			8.1	48.6	29.7	**8.1**	**5.5**
7	6.9	20	26.7	**3.3**		9.1	45.5	21.2	**18.2**	**6.1**
8	7.7	30.8	38.5	**23.1**		12.5	31.3	43.8	**12.5**	

Table-5. Pattern of Xerostemia

	Honey Treated Arm					Control Arm				
Weeks	**0**	1	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
1	88.1	11.9				88.3	11.7			
2	52.5	44.1	3.4			53.4	46.6			
3	37.7	54.7	5.7	**1.9**		28	66	6		
4	20.8	64.4	12.5	**2.1**		20.9	60.5	18.6		
5	19	54	23.8	**2.4**		7.7	53.8	33.3	**5.1**	
6	8.6	62.9	22.9	**5.7**		8.1	48.6	35.1	**8.1**	
7	7.1	53.6	21.4	**14.3**	**3.6**	12.5	40.6	28.1	**18.8**	
8	7.1	57.1	14.3	**21.4**		6.3	37.5	43.8	**12.5**	

Change oh body weight

The regular body weight measurement revealed a gradual reduction in the body weight (median 5 kg) Table-6.

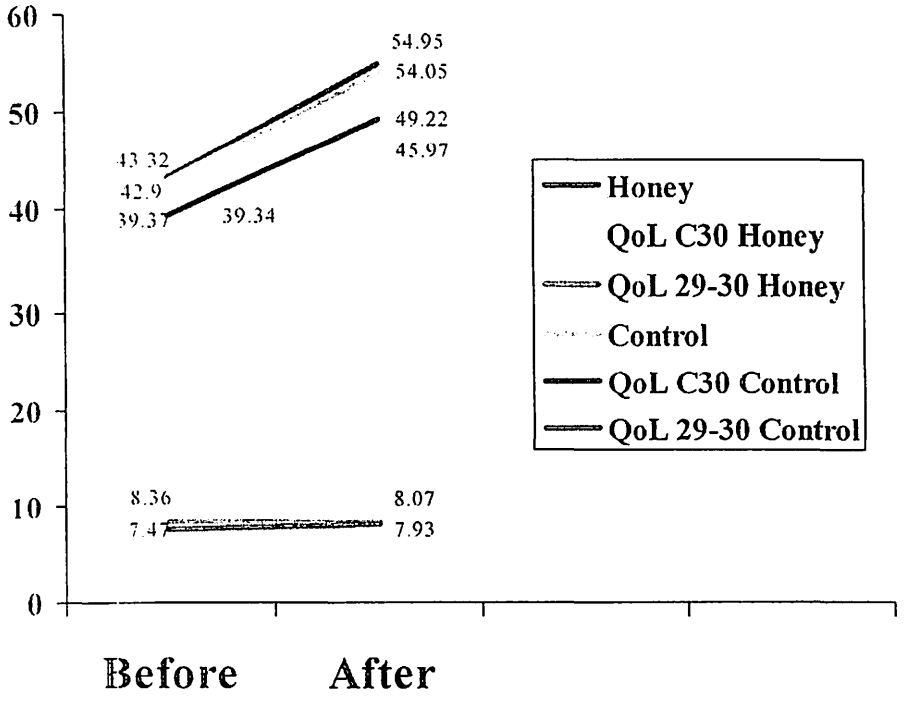
Table-6. Change of body weight during radiotherapy

	Honey		Placebo	
	Mean in Kg	Median in Kg	Mean in Kg	Median in Kg
Week.1	60.16	61.4	59.41	60.4
Week.2	58.94	59	58.28	59
Week.3	57.82	58.75	57.26	57.55
Week.4	54.98	57	55.97	57.2
Week.5	54.34	54.25	54.48	55.4
Week.6	52.82	52.5	52.99	52.15
Week.7	51.4	51	49.47	49
Week.8	53.8	55	54.93	54.4

Change in the quality of life

The general quality of life was evaluated using EORTC general quality of life questionnaire. There was about 10% difference in the quality of life before and after treatment in both placebo and honey treated group of patients (Fig-3). The deterioration of EORTC C30 QlQ was less marked in honey treated arm than controls.

Figure-3.Comparative QoL graph show slope of EORTC H&N and general QoL



Discussion

Oral mucositis is an acute effect of the radiation exposure to the oral mucosa that exceed tissue tolerance. The above exposure leads to a battery of pathophysiological and immunological consequences that ultimately leads to inflammation, vascularity, and cellular loss, release of cytokine, ulceration, infection and healing. The aim of the radiation mucositis management should be multi-targeted that could prevent various steps of pathogenesis namely initiation, primary damage response, signal amplification, ulceration and healing[6]. In this study we utilized pure natural honey in the prophylactic management of chemoirradiation-induced mucositis amongst nasopharyngeal cancer patients. There was non-compliance to honey and placebo treatment due to non-palatability and compliance to honey and placebo agents leading to increased dropout of patients in the evaluation. There was no significant improvement in the mucositis

amongst honey treated group of patients. However there was a trend towards reduction incidence of RTOG grade-3-4 mucositis among honey treated group of patients compared to controls. These findings could be less number of patients compliant to honey and placebo treatment. The evaluation of body weight too showed equivocal reading in honey and control group of patients.

Management of oral mucositis is changing. A huge number of agents and methods have been practiced in clinical trials, however, none of the agents or methods have shown significant benefit to reduce radiation induced mucositis. In one of the meta-analysis by Wothington et al 5-agents has been indicated to have some benefit in oral mucositis such as placental extract, benzydarmine, antibiotic lozenges, glutamine and oral cooling agents those warrant further clinical trial[10]. The difficulties in the understanding of the results of such trials have been further complicated due to the adoption of different types of mucositis grading system used by individual investigators. The WHO, RTOG, NCI-CTC grading systems are most often used in the past, however they are not reproducible and inter-observer variation of reporting might be great. Most of the trials do not include dental or oral surgeons in their trials. Very recently oral mucositis assessment score (OMAS) have been devised to report mucositis objectively. The oral cavity is divided in to 9 sub-sites namely 1.upper labial mucosa, 2.lower labial mucosa, 3-4 right and left buccal mucosa, 5.right and 6.left lateral and undersurface of the tongue, 7.floor of the mouth, 8.hard-palate and 9.soft-palate. The radiation mucositis are graded as redness or ulceration in each site. The combination of erythema and ulceration are considered as OMAS score. It need training and education among participating investigators to report accurately. A study conducted amongst 65 investigators showed consistent reporting[11].

Honey is known to be antibacterial due to release of H2O2 at the tissue site, reduce inflammation, promote tissue repair, add nutrition and inhibit many complimentary cascade pathways of mucositis pathogenesis[12]. Honey act in mucositis in multiple steps of mucositis thus help alleviation of discomfort on various steps of mucositis.

In a recent randomized study by Rashad et al[13] from Saudi Arabia studied the role of topical honey on the prophylaxis against chemoradiotherapy-induced mucositis. They studied the alteration of mucositis pattern among 20-oropharyngeal cancers on chemoradiotherapy treatment compared to controls receiving similar radiotherapy protocols. The patterns of oral pathogens were also reviewed. In their study they noticed significant reduction of severe mucositis ($p<0.005$). Candida colonization and aerobic pathogen bacterial culture was reduced significantly in honey treated arm compared to matched controls.

Another study from Iran by Motallebnejad and colleagues[14] studied the development of oral mucositis among head and neck cancer patients on radiotherapy using specific OMAS index . In their study arm, patients received 20 ml of natural honey 15minutes before radiotherapy, 15 minutes after radiotherapy and 6 hours after radiotherapy. The age matched control patients were treated with saline oral rinse. The mucositis score on OMAS scale was significantly reduced among honey treated patients 20 vs 8 at the end of 6^{th} week of radiotherapy. The mean weight loss in both groups was analyzed using the independent sample t-test which was significantly high amongst controls group of patients (p 0.0000).

In our earlier study on the role of topical honey in radiation mucositis amongst 40 head and neck cancer patients. We showed significant reduction in RTOG grade3-4 severe mucositis compared to controls. Instead of loosing weight, static or positive weight gain was observed in the study arm[8]. Similar study in Japan revealed benefits of pure natural honey in the painful stomatitis caused by radiation mucotitis[9]. Smirnova et al from Russia studied to role of dagree "honey laminolact"to reduce post radiotherapy intestinal complication among pelvic tumors undergoing radiotherapy[15].

The use of honey in cancer is widespread. In a pilot study, honey dressing was superior to compared paraffin dressing in terms of tame taken to healing. The authors suggested more recruitment of patients to get better statistical difference. The study was prematurely closed due to less recruitment of cases, more follow up time required to evaluate response to intervention[16].

Quality of life was evaluated using standard EORTC general and head and neck specific quality of life. There was similar deterioration in the quality of life in both honey and placebo group of patients.

Radiation mucositis is known to cause oropharyngeal pain leading to dysphagia and decreased intake. The nutrition is further complicated by the loss of taste and feeling of nausea and vomiting and cancer induced anorexia. The resultant malnutrition leading to weight loss (cachexia) and non-compliance to radiotherapy or chemotherapy . In our study we observed median weight reduction of ~10Kg over the period of irradiation. In a comparative study suing honey and no treatment the mean weight loss was 1 0.35 (0-7Kg); whereas in the control group the mean weight loss was 6.3 0.53 (2-11Kg). The above difference was statistically significant[14]. In various studies in concurrent chemo-radiotherapy in head and neck cancers investigators advise total parenteral nutrition to combat weight loss[17], however we did not used any parenteral or enteral feeding.

In conclusion, the current study did not showed significant mucositis changes perhaps because of incomplete data from participating centers due to discontinuance of honey treatment in the middle of radiotherapy. The main complaint was nausea and vomiting and some patients complained of burning sensation on mucosa. The above effects might be due to poor quality of honey or peculiar response of concurrent chemoradiotherapy-induced mucositis. Further studies are needed with established mucositis scale to observe any significant benefit in mucositis.

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Randomization No: | | |

IAEA Research Project: Phase-III Randomized trial comparing topical application of natural honey in the management of radiation mucositis among patients undergoing radical radiotherapy for nasopharingeal cancer.

Name of the patient: _____

Identity Card Number/Passport Number: | | | | | | | | | | | | |

Hospital Number: | | | | | | | | | | | |

Age (in years): | |

Sex : M / F

Race: _____

Any other non-concerous medical problem: _____

Perevious anticancer treatment history

Diagnosis: Nasopharyngeal Cancer.

Stage (TNM-AJCC system)

Histology (Tissue diagnosis) with reference number

Oro-dental hygiene: loose teeth/ gingivitis/ caries/ edentulous/ Use of denture during treatment.

Check list

Full blood count (Hb%, TLC and Platelet)
Liver function test
Kidney function test
Pretreatment EORTC QoL-C30 and QoL Head & Neck 35 questionnaire
Written consent

Radiotherapy Details

Fields and field sizes

Parallel opposed lateral alone

Parallel opposed lateral and lower anterior

Phases of radiotherapy

Total dose in Gy

Fractionation schema

Dose per fraction

Overall treatment time

Treatment breaks (In days and reason)

Intra-Radiotherapy Evaluation (Please use RTOG grading system and same weighing machine)

Dates	Week-1	Week-2	Week-3	Week-4	Week-5	Week-6	Week-7	Week-8	Week-13/14
Oral mucositis grade (RTOG)									
Dysphagia grade (RTOG)									
Body Weight (in Kg)									
Dry mouth									

Post-radiotherapy assessment on the last day
QoL C-30 and QoL H & N 35 questionnaire

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you had trouble eating?	1	2	3	4
50. Have you had trouble eating in front of your family?	1	2	3	4
51. Have you had trouble eating in front of other people?	1	2	3	4
52. Have you had trouble enjoying your meals?	1	2	3	4
53. Have you had trouble talking to other people?	1	2	3	4
54. Have you had trouble talking on the telephone?	1	2	3	4
55. Have you had trouble having social contact with your family?	1	2	3	4
56. Have you had trouble having social contact with friends?	1	2	3	4
57. Have you had trouble going out in public?	1	2	3	4
58. Have you had trouble having physical contact with family or friends?	1	2	3	4
59. Have you felt less interest in sex?	1	2	3	4
60. Have you felt less sexual enjoyment?	1	2	3	4

During the past week:	No	Yes
61. Have you used pain-killers?	1	2
62. Have you taken any nutritional supplements (excluding vitamins)?	1	2
63. Have you used a feeding tube?	1	2
64. Have you lost weight?	1	2
65. Have you gained weight?	1	2

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

RTOG

TOXICITY ASSESSMENT

	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SKIN	No change over Baseline	Follicular,faint,dull Erythema/Epilation/Dry Desquamation	Tender,bright Erythema.Patch. Mod. Edema	Confluent, moist Desquamation Pitting Edema	Ulceration haemorrhage Necrosis
MUCOUS	No Change	Erthema/Mild Pain	Mucositis Sero.Sang.Dis Req.Analgesic	Confluent Fib. Mucositis Req.Narcotic.	Ulceration Hemorrhage Necrosis.
SALIVARY GLAND	No change	Mild dryness mouth Thick Saliva/Metalic Taste	Mod.Dryness Thick Saliva	Complete. Dryness	Acute Salivary Necrosis.
LARYNX	No Change	Mild Hoarseness Mild cough Erythema mucosa	Pers.Hoarseness Refd.Otalgia.Cough. Anti tussive needed.	Whispered Speech Throat pain. Arytenoid.Edema	Marked Dyspnea Stridor. Tracheostomy.
ESOPHAGUS	No change	Mild dysphagia Or Odynophagia	Mod. Dysphagia or Odynophagia	Severe Dysphagia or Odynophagia	.Complete Obstruction Ulceration, Fistula
WBC(X 1000)	> 4.5	3.0 - < 4.5	2.0 - < 3.0	1.0 – 2.0	<1.0
NEUTROPHILS (X 1000)	> 1.9	1.5 – < 1.9	1.0 – < 1.5	0.5 - < 1.0	<0.5 or Sepsis
HEMOGLOBIN (GM %)	>11	9.5 – 11	< 9.5	Paccked cell Transfusion required	
PLATELET (X 1000)	>130	90 – <130	50 – < 90	25 - < 50	<25 or Spontaneous bleeding

	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
NAUSEA/VOMITING	None	Nausea	Transient Vomit.	Requiring Treatment	Intractable Vomiting
DIARRHEA	None	Transient < 2 days	Tolerable >2days	Intolerable Treat. reqd	Hemorrhagic Dehydration
ALOPECIA	None	Minimal	Patchy	complete	non reversible
FEVER	none	< 38 C	38 – 40 C	>40 C	+ Hypotension

Adverse Event	Grade 0	1	2	3	4
Proctitis	none	increased stool frequency, occasional blood-streaked stools or rectal discomfort (including hemorrhoids) not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea requiring parenteral support; rectal bleeding requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain due to radiation.					
Notes: Fistula is graded separately as Fistula-rectal/anal. Proctitis occuring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					
Salivary gland changes	none	slightly thickened saliva; may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	*normal*	*slightly altered*	*markedly altered*	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation
For BMT studies, if specified in the protocol:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonitis
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgensia)	normal	slightly altered	markedly altered	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, and radiographic or biopsy documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile neutropenia.					
Vomiting Also consider Dehydration.	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal - Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

Appendix III

Performance Status Scales/Scores

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints; no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but tires around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

WHOLE ORGAN RADIATION TISSUE TOLERANCES (Emami 1991)			
Organ	TD 5/5	TD 50/5	Endpoint
Bladder	5500	8000	contracture
Brachial Plexus	6000	7500	plexopathy
Brain	4500	6000	necrosis
Brainstem	5000	6500	necrosis
Cauda Equina	6000	7500	plexopathy
Ear			otitis
Esophagus	5500	6800	stricture
Femoral Head	5200	6500	necrosis
Heart	4000	5000	pericarditis
Kidney	2300	2800	nephritis
Larynx	7000	8000	edema
Lens	1000	1800	cataracts
Liver	3000	4000	hepatitis
Lung	1750	2450	pneumonitis
Optic Chiasm	5000	6500	blindness
Optic Nerve	5000	6500	blindness
Parotid	3200	4600	xerostomia
Rectum	6000	8000	proctitis
Retina	4500	6500	blindness
Spinal Cord (>5cm	5000	7000	myelitis
Small Intestine	4000	5500	perforation
Stomach	5000	6500	ulceration
Thyroid	4500	8000	thyroiditis

APPENDIX B

Patient Information and Consent Form

Research Title : **Phase III Randomized Control Trial Comparing Natural Honey in The Management of Radiation Mucositis Among Patients Undergoing Radical Radiotherapy for Nasopharyngeal Cancer.**

Researcher's Name : Dr. Biswa Mohan Biswal

Introduction

You are invited to take part voluntarily in a research study of pure natural honey in the management of radiation mucositis. Honey is a mixture of flower nectar and the body part of honey bee. Honey is an old remedy in many disease including burn and oral disease. Recent studies shows that pure natural honey can prevent the development of severe year radiation mucositis. Honey being a nutritional supplement rich in calorie, help cancer patient to gain energy. We are going to use honey to a group of patients undergoing radiotherapy that aimed to prevent mucositis. Before agreeing to participate in this research study, it is important that you read and understand this form. It describes the purpose, procedures, benefits, risks, discomforts, and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at anytime. If you participate, you will receive a copy of this form to keep for your record.

Your parcipation in this study is expected to last up to 6 - 8 weeks. Up to 120 patients will be participating in this study.

What is nasopharyngeal cancer?

Nasopharyngeal cancer is one of the most common cancer among Malaysian men arising from the nasopharynx. The nasopharynx is present behind the nose and at the top of the throat. This cancer is very common among Chinese and Malay race. Once started, it can spread to neck nodes and than to other parts of the body if not treated by radiotherapy.

What is mucositis?

Mucositis is the common symptom develop among patients those undergoing radiotherapy to the head and neck area. There may be symptoms of sore throat, painful swallowing and ulceration of the inner linning of the mouth and throat.

Purpose of the Study

The purpose of this study are to determine if pure natural honey can prevent the development of symptomatic radiation mucositis.

Qualification to Participate

The doctor in charge of this study or a member of the study staff has discussed with you the requirements for participation in this study. It is important that you are completely truthful with the doctor and staff about you health history. You should not participate in this study if you do not meet all qualifications.

Some of the requirements to enter in this study are –

- Nasopharyngeal cancers.
- HPE evidence of cancer.
- Wiling to sign consent form to participate.
- Willing for full course of radical radiotherapy.

You cannot participate in this study if

- You receive previous radiotherapy.
- You are suffering from Co-morbid connective vascular diseases, diabetes.
- Insane person.

Study Procedures

At your first visit ,if you agree to participate in this study the doctor incharge will perform routine clinical examination, review your x-rays, biopsy report and other relevant investigation necessary for you.If you are selected for radical radiotherapy, you will be asked to answer our questions to assess your wellbeing. Radiotherapy treatment consist of five treatments per week to a total of 7 – 8 week. The patient in this study group will be given 20 ml of pure natural honey, 15 minutes before radiotherapy, 15 minutes after radiotherapy and 6 hour after radiotherapy. During the period of radiotherapy your doctor / research assistant will check your oral cavity for the development of mucositis everyweek. We record your body weight everyweek during the course of radiotherapy.

Following the treatment, the study doctor or his representatives may contact you to obtain information about your experiences during the trial or the status of your health and quality of life.

Risks

Honey is the natural product being used for food supplement don't have any significant additional side-effect unless you are allergic to honey. Radiotherapy to the head & neck area carries similar risks to both study and control arm.

Reporting Health Experiences.

If you have any injury, bad effect, or any other unusual health experience during this study, make sure that you immediately tell the nurse or Dr. Biswa Mohan Biswal at 09-7663208 @ HP. 019-9669165. You can call at anytime, day or night, to report such health experiences.

Other Treatments

If you do not want to take part in this study, your illness or condition will be treated with radical radiotherapy alone. The study doctor can discuss these treatments and therapies with you.

Participation in the Study

Your taking part in this study is entirely voluntary. You may refuse to take part in the study or you may stop participation in the study at anytime, without any penalty or loss of benefits to which you are otherwise entitled.

Your participation also may be stopped by the study doctor or sponsor without your consent.

If you stop being part of this study, the study doctor or one of the staff member will talk to you about medical issues regarding the stopping of your participation.

Possible Benefits

Study agent will be provided to you at no cost to you. You may receive information about your health, physical examination finding and laboratory tests to be done in this study.

Although honey being used for the radiation mucositis, there is no guarantee that you will receive any medical benefit.

Questions

If you have any question about this study or your rights, please contact ;

1. Dr. Biswa Mohan Biswal.MD, Consultant Clinical Oncologist
Department of Nuclear, Medicine,Radiotherapy & Oncology
Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
09-7663208 (Office), HP: 019-9669165,
(email biswa@kb.usm.my)

2. Dr. Gurcharan Singh Khera, Consultant Clinical Oncologist Damasara Specialist Hospital.119. Jalan ss 20/10 Damansara Utama, 47400 Petaling Jaya, Selangor, Malaysia.
03-77223880 (Office), HP: 012-3865140
(e-mail: guru1@tm.net.my)

3. Dr. C.R Bina Devi, Consultant Clinical Oncologist
Department of Radiotherapy & Oncology
Hospital Umum, Kuching, Sarawak.
(e-mail: devina@pc.jaring.my)

4. Prof. Madya Yoke Ching Foo.Associate Professor (UPM) & Clinical Oncologist.
Department of Radiotherapy & Oncology, General Hospital Kuala Lumpur
Jalan Pahang, Kuala Lumpur.
(e-mail: y.c foo @ hotmail.com)

Confidentialty

Your medical information will be kept confidential by the study doctor and staff and will not be made publicly available unless disclosure is required by law.

Data obtained from this study that does not identify you individually will be given to the investigation and/or its representatives and may be published

Your original medical records may be reviewed by the sponsor and/or its representatives, the Ethical Review Board for the this study, and regulatory authorities.

By signing this consent form, you authorize the record review, information storage and data transfer described aboved.

Signatures

To be entered into the study, you or a legal representative must sign and date the signature page (see Appendix 1)

Appendix 1

Patient Consent Form (Signature Page)

Research Title : Phase III randomized control trial comparing natural honey in the management of radiation mucositis among patients undergoing radical radiotherapy for nasopharyngeal Cancer.

Researcher'S Name : Dr. Biswa Mohan Biswal

To become a part this study, you or your legal representative must sign this page.
By signing this page, I am confirming the following:

- I have read all of the information in this Patient Information and Consent Form including any information regarding the risk in this study and I have had time to think about it.
- All of my questions have been answered to my satisfaction.
- I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.
- I may freely choose to stop being a part of this study at anytime.
- I have received a copy of this Patient Information and Consent Form to keep for myself.

Patient Name (Print or type)	Patient Initials and Patient Number
Patient I.C Number **(new)**	**Patient I.C** No. **(old)**
Signature of **patient** or Legal Representative	**Date** (ddMMyy) (add ime of day if appropriate)
Name & Signature of Individual Conductiong Informed Consent Discussion (Print or Type)	**Date** (ddMMyy)
Name & Signature of witness	**Date** (ddMMyy)

Notes: