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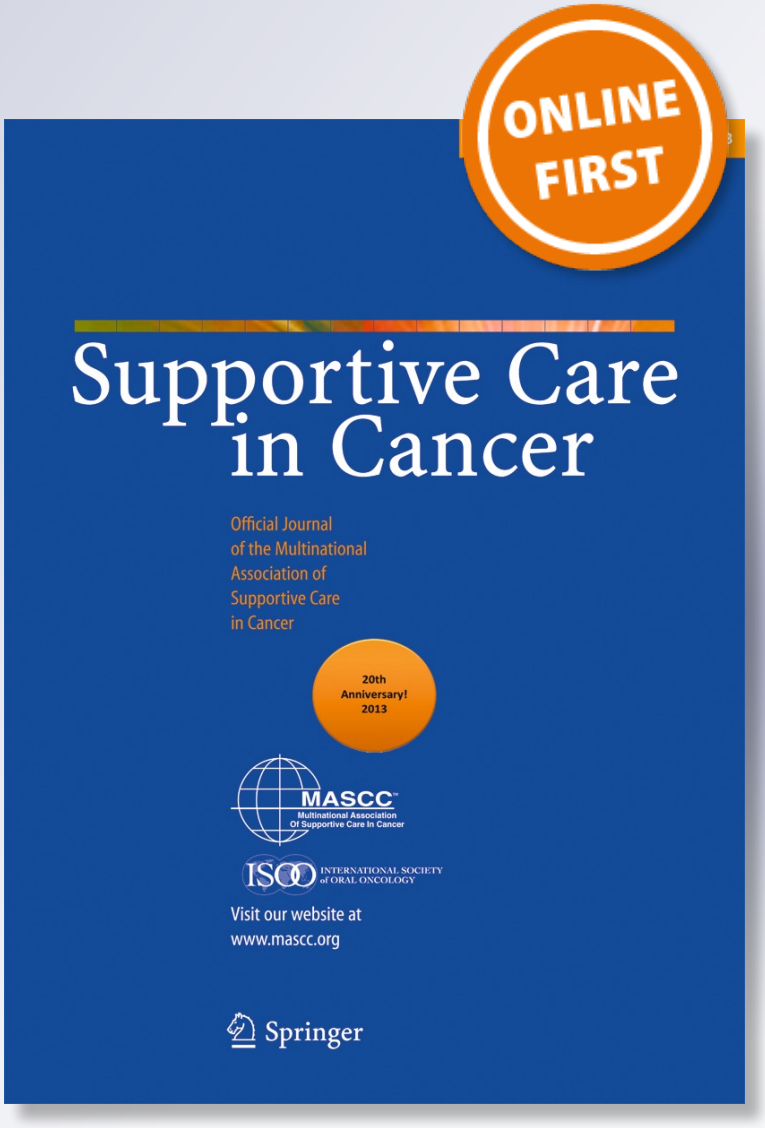

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ORIGINAL ARTICLE

A randomized placebo-controlled trial of manuka honey for radiation-induced oral mucositis

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Abstract
Background Few treatments have the potential to reduce the severity of radiation-induced mucositis in head and neck cancer patients. Some small studies have suggested that organic honey may be a useful preventive treatment.
Methods This investigator-initiated double-blind randomized placebo-controlled trial investigated whether honey reduced the severity of radiation-induced oral mucositis (ROM). One hundred six head and neck cancer patients from the Vancouver and Sudbury Cancer Centers in Canada were randomized to swish, hold, and swallow either 5 ml of irradiated organic manuka honey or a placebo gel, four times a day throughout radiation treatment, plus seven more days. Severity of oral mucositis according to the Radiation Therapy Oncology Group (RTOG), World Health Organization (WHO), and Oral Mucositis Assessment Scale scales, weight, and subjects' symptom severity and quality of life were assessed weekly. Sialometry was performed at baseline and at the last study visit.
Results One hundred six patients were recruited. Twenty-four did not attend any mucositis assessments. One was removed from the study because of off-study consumption of store-bought manuka honey. The remaining 81 patients had at least one mucositis assessment and were included in the analysis. Sixty-two percent of subjects received concurrent chemotherapy; 81 % were male. The groups were well-matched, and blinding was excellent. Dropouts were mostly due to nausea and were similar in both arms, with 78 % being able to tolerate the study products for more than 1 week. The dropout rate was 57 % in those who received honey and 52 % in those who received placebo gel. The dropout rate in those who had concurrent chemotherapy was 59 % and in those who only received radiation was 47 %. There was no statistically significant difference between the honey and placebo arms in any of the outcome indicators. Those who completed the study in both treatment arms had low rates of RTOG greater than or equal to grade 3 mucositis; 35 % in the honey group and 43 % in the placebo group.
Conclusion Despite promising earlier reports, manuka honey was not tolerated well by our patients and, even when used as directed, did not have a significant impact on the severity of ROM.

Keywords Radiotherapy · Mucositis · Honey · Quality of life · Randomized · Placebo-controlled

Background

Oral mucositis is one of the most unpleasant side effects of head and neck radiotherapy. Despite testing of a number of promising agents, no treatments have been conclusively shown to prevent or treat mucositis other than analgesics [1, 2]. The burden of radiation-induced oral mucositis (ROM) depends on its severity and duration, the quality of supportive care, and the coping skills of the individual. However, even moderate oral mucositis has a major impact on nutrition, quality of life, and the patient's ability to complete the prescribed radiotherapy (RT) [3].

Severe ROM is associated with higher doses of radiation, altered fractionation schedules, and the use of concomitant chemotherapy (CRT). There is also unexplained variability

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between individuals undergoing identical treatments [4]. The prevalence of severe ROM varies widely in the literature and appears to be changing as new treatment patterns evolve, particularly with the more widespread use of CRT and the use of intensity modulation (IMRT). The pathophysiology of ROM has only recently been appreciated and is complex, involving the generation of reactive oxygen species (ROS) which then stimulate a number of transcription factors leading to DNA damage and subsequent cell death. One transcription factor (NF-κB) appears to play a key role in upregulating genes which express pro-inflammatory cytokines, leading to apoptosis and tissue injury. Other genes are also upregulated, leading to activation of the COX-2 pathway and the promotion of angiogenesis. ROS also activate macrophages, with a simultaneous cascade of inflammation and further tissue injury [5]. Irradiation of the oral cavity and oropharynx often results in substantial alteration of the sense of taste, as well as significant xerostomia. This constellation of symptoms makes the management of ROM particularly challenging.

The largest general survey of mucositis rates was published in 2006 and involved 154 US radiation oncologists and 450 patients. They used a subjective 0–3 mucositis grading system based on investigator judgment. Sixty-six percent of those receiving 50 Gy or greater were rated as having suffered "moderate" (36 %) or "severe" (30 %) mucositis. This included patients having radiation to sites where the symptoms of mucositis can be easier to manage (larynx and hypopharynx) and also included 34 % of patients receiving concomitant chemotherapy of which a total of 76 % experienced either moderate (34 %) or severe (42 %) mucositis [4].

In studies using the Radiation Therapy Oncology Group (RTOG) scale, the reported percentage of patients experiencing grade 3 or 4 mucositis in those receiving radiation of 50 Gy or greater varies widely. In one study of 205 patients receiving ≥50 Gy in either the morning or afternoon, 52.9 and 62.4 % experienced greater than or equal to grade 3 mucositis [6]. In a large negative study of the free radical scavenger amifostine, 35–39 % of 303 patients experienced greater than or equal to grade 3 mucositis. In this study, 44 % of patients had treatment for laryngeal, hypopharyngeal, or unknown primaries. These patients would have been at lower risk of severely symptomatic mucositis than those in whom a significant part of the oral cavity is irradiated, likely explaining the lower reported rates of mucositis [7].

A multinational negative topical microbicidal gel study found that 60–66 % of 545 study patients and 79 % of untreated patients (i.e., no placebo) experienced greater than or equal to grade 3 mucositis. Forty-four percent of these patients had concurrent CT (CRT). The rates for RT and RCT patients were not separately reported [8]. A recent study of 366 patients receiving ≥40 Gy in conventional or hyperfractionated schedules (three out of four with concurrent chemotherapy) used a modified RTOG scale (grade 3 reactions defined as ulcers >1 cm rather than >1.5 cm) and found that 75 % of all patients experienced greater than or equal to grade 3 mucositis [9].

Though there are some agents which are helpful for symptomatic relief, standard care is limited to maintenance of good oral hygiene and (in Canada) use of benzydamine mouthwash (Tantum®) despite weak evidence for its benefit [10, 11]. Though secondary infection (especially by *Candida*) can cause exacerbation of mucositis, significant reduction in mucositis by various antimicrobial substances has not been demonstrated [12, 13]. It, therefore, appears that the mechanism of ROM induction is independent of microbial activity.

Honey

Honey has been used to promote wound healing for centuries. Several recent studies have found honey effective in accelerating wound and burn healing and in treating oral infections. In 2003, a Malaysian report suggested that honey may be very effective in reducing the incidence of grade 3 or 4 oral mucositis for patients receiving head and neck radiation [14]. In this study, 40 patients receiving 60–70 Gy to the oropharyngeal mucosa were randomized to RT plus 20 ml honey from bees fed on manuka three times a day or RT alone. No placebo was used. Dramatically, only 20 % of the honey-treated group had peak mucositis severity of RTOG greater than or equal to grade 3, vs. 75 % in the control group. The honey-treated group also lost less weight and experienced less radiotherapy treatment interruptions.

Honey has several antimicrobial qualities, including high osmolality, low pH, and ability to generate noncytotoxic levels of hydrogen peroxide through the enzyme glucose oxidase. Manuka pollen is collected by honey bees from the manuka tree (*Leptospermum scoparium*). Manuka honey has additional potent antibacterial effects attributed to the phytochemical component methylglyoxal [15]. Though antimicrobial agents have been found to have no effect on reducing mucositis, it is important to know that honey will not increase oral microbial growth which could exacerbate mucositis. Honey is, in fact, an excellent antimicrobial agent, including having an effect against antibiotic-resistant organisms [16].

A New Zealand study found manuka honey to be effective in reducing plaque and gingivitis. Despite its sugar content, studies have shown that the high antibacterial activity of this honey is anticariogenic. When applied to radiation-induced xerostomic oral mucosa, honey also increases the microhardness of tooth enamel, thus acting to prevent caries [17].

The suggested mechanism of action of honey in mucositis is through its positive effect on cell epithelialization and regrowth. There are a number of good studies demonstrating that honey is effective in promoting wound healing when applied as a dressing [18]. The low-level enzymatic hydrogen peroxide generation (which has antimicrobial effects) also appears to be responsible for part of this healing effect, though

this is not well understood. There are also non-hydrogen peroxide phytochemical mechanisms which appear to be involved in wound healing, especially in manuka honey. Too high a hydrogen peroxide level could, however, potentially cause oxidation and actually worsen cell damage. Glucose oxidase activity, and thus hydrogen peroxide generation, is actually greater in diluted honey than in full-strength honey [19]. Different honeys seem to have different antimicrobial potentials, but manuka honey appears to be the most potent [16] and is the type of honey most commonly used for medical purposes and is widely available around the world.

There is a possibility of contamination of honey by yeasts and molds which are resistant to the antimicrobial activity of the honey. There is also the rare but potentially life-threatening possibility of *Clostridium botulinum* contamination. This has led to caution in the use of unpasteurized honey, especially for immunocompromised hosts. The hydrogen peroxidase-generating property of honey is, however, heat-sensitive and is decreased by pasteurization. Irradiation with 25 kGy of radiation has been shown to kill *C. botulinum* spores without destroying the antimicrobial activity [20, 21]. Certified organic honey is also free of any antibiotic, pesticide, or other chemical residues which might have potential for harm.

Methods

Study design

This study was a randomized placebo-controlled trial with two arms: experimental treatment consisting of topical manuka honey four times a day and a control arm of topical placebo gel four times a day. Patients in both arms received instructions for standard oral hygiene. The study also gathered additional efficacy and health-related quality of life data points. Oral mucositis was assessed using three commonly used scales (RTOG, Oral Mucositis Assessment Scale [OMAS] [22], and World Health Organization [WHO] severity scales). The study started recruiting at the Vancouver Cancer Centre in 2008 and the Sudbury Cancer Centre joined as a second site in 2010.

Patients were included if they were to receive radiation therapy of 50 Gy or greater, with the dosage field affecting the oral mucosa in a minimum of three visible sites, and were willing to attend weekly assessments throughout their treatment, plus at least 1 week after completion of treatment. They were excluded if not competent to consent, participating in other clinical trials which might affect the severity of mucositis, or allergic to honey, multiple pollens, or celery.

Method of recruitment

Patients diagnosed with head and neck cancer visit the dental clinics at the cancer centers for a comprehensive oral exam prior to initiating radiation treatment. At this visit, a full periodontal exam is done. Any teeth requiring extraction, caries control, or periodontal care prior to commencing radiation therapy are identified and the required treatment is scheduled. At this appointment, the consequences of radiation therapy with regards to its effects in the mouth are explained. Oral hygiene instructions are reviewed with each patient, including fluoride therapy and moisturization of the mouth. Patients were recruited to the study during this visit by either the dental resident or the attending oral medicine specialist/dentist in the clinic. The person obtaining consent was the person who conducted the initial (baseline) oral exam.

Patients usually commence therapy between 1 and 6 weeks after this visit, depending on their individual circumstances. Subjects had until the commencement of their radiation therapy to decide whether or not to participate. The study product was dispensed before the patient's first radiation treatment so they could start it on their first treatment day. Approval to carry out this study was provided by Health Canada, the University of British Columbia/BC Cancer Agency Ethics Review Board, and the Northeast Cancer Centre Ethics Review Board. The study was registered with clinicaltrials.gov; NCT006154240.

Randomization

A treatment allocation schedule with balanced randomly permuted blocks was prepared by a statistician. The randomization was stratified to ensure balance between the two treatment groups with regard to the expected 30 % of patients who would receive concurrent chemotherapy. The hospital pharmacies dispensed sachets of study product marked A or B consecutively according to the schedule. The study was blinded to all except necessary pharmacy staff until after the study was closed. An external study monitor was appointed.

Study procedures

All patients were given instructions to use a basic oral rinse (1 tsp. table salt with 1 tsp. baking soda in 1 L of tap water; 0.9 % saline and 0.5 % sodium bicarbonate) four times a day after meals and after radiotherapy on treatment days or at approximately the same time on nontreatment days. They were also instructed to apply topical fluoride treatment at bedtime at least 30 min after the honey/placebo gel to maximize the fluoride's effectiveness and to minimize dilution effect of both substances.

The honey and placebo gels were provided in single-use 5-ml sachets and were to be taken after every oral rinse, i.e., four times a day. Subjects were instructed to pour the product into their mouths directly from the sachets, to circulate the gel in their mouth for at least 30 s, and then to swallow. Subjects were instructed not to eat, drink, or rinse their mouths for

30 min after each application. Treatment started on the first day of radiation and was requested to continue to include the 7 days following the last radiation treatment. To assist with maintenance of blinding, subjects were asked not to discuss the taste or presentation of their study treatment with any clinicians or with other patients.

All subjects were requested to visit the oral oncology/dentistry department of the cancer center on the first day of their treatment and then on the same day of the week (or closest possible) until mucositis had resolved. At these visits, the subjects were weighed, were asked to complete a brief questionnaire, and underwent an oral examination conducted by a qualified observer. The same oral examination was carried out for simultaneous rating using all three mucositis severity scales (RTOG, OMAS, and WHO) (Table 1). Since the RTOG scale was the primary scale for this study, it was always completed first. The order of completion of the OMAS and WHO scales was randomly assigned to each patient visit with a 0.5 probability. The qualified observers at each site were separately trained prior to the start of the study and communication was made between site leaders to ensure consistency of rating between observers.

Unused treatment medication was collected at the last visit in order to measure compliance. Diabetic patients were asked to monitor their blood sugar readings closely during radiation treatment. If blood sugar readings were above their normal levels and could not be improved satisfactorily by modification of the diabetes treatment regimen, then the patient was withdrawn from the study.

Study products

Certified organic manuka honey (active 16+) was derived from Canterbury area of New Zealand and supplied by Wedderspoon Organics, Duncan, BC, Canada, in single-use 5-ml pouches. The identical sealed pouches were gamma-irradiated using a dose range of 25 to 35 kGy at a Health Canada-approved and FDA-approved commercial facility. The pouch material was gamma-irradiated and included a tear notch for easy opening. Random samples of the honey and placebo sachets were tested for bacterial contamination prior to any administration to patients and were retested part way through the study.

The sugar-free placebo gel was supplied by a Vancouver commercial pharmacy following taste testing of a variety of "recipes" by healthy volunteers. A 6 % mixture of methyl cellulose was mixed with "Oral Base Sugar Free" (Transderma Pharmaceuticals Inc., Coquitlam, BC, Canada) in equal amounts. Oral Base contains the following ingredients: water 80.10 %, sorbitol 10.00 %, glycerin 9.00 %, Natrosol 250 HR 0.35 %, sucralose (Splenda) 0.10 %, methylparaben 0.01 %, carboxymethyl cellulose 0.01 %, and xanthan gum 0.01 %. Small amounts of potassium sorbate,

Table 1 Comparison of mucositis severity scales

Grade	0	1	2	3	4	5
WHO	None	Soreness± erythema	Erythema, ulcers, and patient can swallow solid food	Ulcers with extensive erythema and patient cannot swallow solid food	Mucositis to the extent that alimentation is not possible	
RTOG	None	Erythema of the mucosa	Patchy reaction <1.5 cm, noncontiguous	Confluent reaction >1.5 cm, contiguous	Necrosis or deep ulceration±bleeding	
OMAS worst site score (erythema 0–2 and ulceration 0–3)	No erythema or ulceration	Mild erythema or ulceration <1 cm^2	Mild erythema and ulceration <1 cm^2	Mild erythema and ulceration 1–3 cm^2 or severe erythema and ulceration <1 cm^2	Severe erythema and ulceration 1–3 cm^2 or mild erythema and ulceration >3 cm^2	Severe erythema and ulceration >3 cm^2

citric acid, simethicone, grape flavor, and color were added. The final concentration of methyl cellulose was 3 %.

None of the placebo ingredients are known to have any effect on mucositis or oral infection and do not have any nutritional value. The amount of sorbitol is the minimum required for palatability and would not have any effect on bowel function. The placebo was a clear yellowish gel with the consistency and taste similar to natural honey, but less sweet. Manuka honey has a strong and slightly medicinal taste, different from the usual "supermarket" honey. Though the placebo and honey were not identical, they were described to subjects as "honey-based" rather than as "honey." On testing among a convenience sample of volunteers, both products were found to both be plausible "honey-based gels."

Table 2 Patient characteristics

	Honey arm		Placebo arm		*p* value
	Characteristic	*N*	Characteristic	*N*	
Male	81 %	54	84 %	50	0.7345[a]
Mean age (years)	56.8	52	59.5	48	0.02317[b]
Mean weight (kg)	85.6	52	79.6	50	0.0859[b]
Diabetic	3 (6 %)	52	10 (20 %)	49	0.0281[a]
Smoker	9 (18 %)	51	7 (14 %)	49	0.6467[a]
ECOG >0	8 (15 %)	51	13 (25 %)	48	0.0930[c]
Chemotherapy	31 (57 %)	54	35 (67 %)	52	0.2932[a]
RT ≥7,000 Gy	36 (68 %)	53	30 (58 %)	52	0.2780[a]

[a] Chi-square test

[b] Two-sample *t* test

[c] Fisher's exact test

Statistical methods

The primary hypothesis to be tested was whether administration of regular topical oral application of manuka honey would reduce the severity of oral mucositis compared to the placebo control arm. Evaluable mucositis severity was defined as having at least one mucositis assessment following baseline. The primary efficacy endpoint was the proportion of patients reaching RTOG grade 3 mucositis at any point during the study on the honey arm vs. the placebo arm. The difference in the proportions was obtained and assessed using a one-sided 95 % confidence interval.

Combining information from the available applicable literature and estimates by our oncologists, we estimated that at least 55 % of patients receiving RT alone and at least 75 % of those receiving CRT would experience RTOG greater than or equal to grade 3 mucositis. The study was designed to recruit up to 180 subjects and randomize them equally into the two study arms. Randomization was stratified by adjuvant treatment (concurrent chemotherapy or not) and by cancer center (Vancouver or Sudbury). Since there was no standard care for oral mucositis, a one-sided alternative hypothesis was used. If our estimates of mucositis severity and percentage receiving concurrent chemotherapy were correct, then the expected rate of RTOG greater than or equal to grade 3 mucositis in the control arm overall would be 67 %. With 180 subjects, the study would be powered to detect a 29 % reduction (i.e., to 48 %).

The preliminary study by Biswal et al. reported a reduction in the proportion of RT-only patients experiencing RTOG greater than or equal to grade 3 from 75 to 20 %. The possibility of a dramatic reduction of this nature was taken into consideration by having a preplanned interim analysis at 50 % of target recruitment.

The exploratory purposes of the study were to document the normal course of mucositis throughout radiation and chemoradiation treatment, using the RTOG, OMAS, and WHO severity scales. Overall severity of mucositis was assessed by the area under the curve (AUC) using each mucositis grade. This was derived from the sequential oral assessments conducted at the baseline visit and every 7 days until the last study assessment. A minimum of two mucositis assessments were required to perform this AUC analysis.

Symptom severity was measured by the overall mouth and/or throat pain as measured on a 0–10 scale, with 10 being the worst possible and 0 being no pain. Self-reported ability to eat was measured on a five-point scale: 0=not limited, 1=limited a little, 2=limited some, 3=limited a lot, and 4=unable to do. The change from baseline was calculated for each weekly assessment and dichotomized into change <2 and change two or more. The dichotomized change in ability to eat was analyzed using a generalized estimating equation with a logistic link function and an unstructured covariance matrix. Self-reported ability to drink was measured on an identical five-point scale and analyzed the same way.

Demographic and baseline factors were considered for inclusion in all analyses. Additional prespecified exploratory outcomes, including any correlation between symptom severities, quality of life, and weight loss with the RTOG, WHO, and the four ways of calculating/reporting OMAS

Table 3 Cancer site

	Honey (*N*=54), *N* (%)	Placebo (*N*=52), *N* (%)
Hypopharynx	2 (3.7)	3 (5.8)
Larynx	6 (11.1)	9 (17.3)
Nasopharynx	8 (14.8)	5 (9.6)
Oral cavity	16 (29.6)	18 (34.6)
Oropharynx	21 (38.9)	19 (36.5)
Unknown	1 (1.9)	2 (3.8)

Multiple sites could be specified for each patient

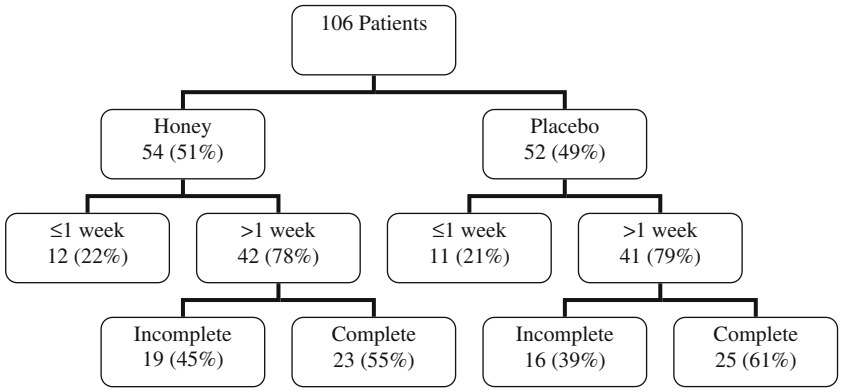

Fig. 1 Study flowchart

assessments, were reported separately. Randomized patients who had at least one mucositis assessment were included in the intent-to-treat (ITT) analysis and classified according to their assigned treatment group.

Results

The planned interim analysis was initiated after the 90th subject had been recruited, and the study kept recruiting until the results of the analysis were available. Total final recruitment was 106 patients. At this time, there were significant concerns about the recruitment rate and high number of subjects dropping out of the study, primarily due to nausea. Though the nausea was caused by the radiation±chemotherapy and not primarily by the study products, both honey and placebo tended to cause gagging and worsening of nausea because of the strong taste and thick consistency. Also, with increasing awareness of the prior studies' positive results, decreasing numbers of patients seemed prepared to take the risk of being assigned placebo, and manuka honey was becoming widely available in health food stores. One patient admitted trying store-bought manuka honey and was removed from the study. His data were excluded from the analysis.

Assuming that the placebo had a rate of peak RTOG ≥3 of 45 %, with 81 subjects with more than one mucositis severity assessment, the study had 80 % power to detect a 29 % difference in the peak RTOG between the placebo and the manuka honey treatment arms at the 5 % significance level. It was felt that it would not be realistically possible to recruit and retain the intended 180 subjects in a reasonable time frame. Our external monitor, therefore, recommended that we terminate the study. Recruited patients who were on study at the time of the analysis were allowed to continue the study if they so chose. No subjects were terminated from the study involuntarily.

As shown in Table 2, the majority of subjects were male, and <1 in 5 were smokers. The ethnicity of both groups was much the same: 69 and 71 % of subjects being of Caucasian background in the honey and placebo arms, respectively, and four of each group being Asian. The honey arm group was slightly older than the placebo arm; however, the placebo arm had more diabetic patients and more patients with poor performance status. As shown in Table 3, both groups were well matched for cancer location, with the majority of treatment sites being the oral cavity or oropharynx. At 62 %, more than twice the number of patients than we had expected received CRT with slightly (but not statistically significantly) more patients receiving chemotherapy in the placebo arm than the honey arm. This was countered by the honey arm patients receiving a slightly higher mean dose of radiation than the placebo arm. There was no significant difference in the number of radiation fractions in each arm ($p=0.2636$, data available on request).

Table 4 Dropout rates by study arm

Treatment	Completed study			Dropout rate (%)
	No	Yes	Total	
Honey	31	23	54	57.4
Placebo	27	25	52	51.9
Total	58	48	106	54.7

Chi-square test, p value=0.5707

Table 5 Dropout rates by treatment modality

Treatment	Completed study			Dropout rate (%)
	No	Yes	Total	
RT	19	21	40	47.5
ChemoRT	39	27	66	59.1
Total	58	48	106	54.7

Chi-square test, p value=0.2452

Table 6 Peak RTOG score

Study arm	Highest RTOG score		Total, *N*	Fisher's exact test *p* value
	<3, *N*	≥3, *N*		
All evaluable patients				0.4126[a]
Honey	26 (65 %)	14 (35 %)	40	
Placebo	23 (56 %)	18 (44 %)	41	
Total	49 (60 %)	32 (40 %)	81	
Patients who stayed on study more than 1 week[b]				0.3222
Honey	20 (65 %)	11 (36 %)	31	
Placebo	17 (54 %)	16 (46 %)	33	
Total	37 (58 %)	27 (42 %)	64	
RT only patients who stayed on study more than 1 week				0.7165
Honey	16 (76 %)	5 (24 %)	21	
Placebo	11 (69 %)	5 (31 %)	16	
Total	27 (58 %)	10 (42 %)	37	
ChemoRT patients who stayed on study more than 1 week				0.7600
Honey	10 (52 %)	9 (47 %)	19	
Placebo	12 (48 %)	13 (52 %)	25	
Total	22 (50 %)	10 (50 %)	44	

[a] Chi-square test was performed

[b] Twenty-one patients stayed in the study for <1 week, 19 did not have an RTOG score, and two had a score of 0

Dropout rate

As seen in Fig. 1, by the end of the first week, just over one in five subjects had dropped out from the study and did not attend for their first follow-up visit. The dropout rate was the same for both honey and placebo groups (see Table 4). Having made it through the first week, a further 39 % of the placebo group and 45 % of the honey group were unable to complete the study. Overall, 57 % of the honey arm and 52 % of the placebo arm dropped out. Patients in the placebo arm tended to have a longer duration on the study than those in the honey arm (median, 31 vs. 22 days). Subjects who did not have chemotherapy tended to stay in the study for a longer period of time than those who had chemotherapy (median, 33 vs. 22 days). As seen in Table 5, the dropout rate for those who received chemotherapy was 59 % overall (61 % in the honey arm and 57 % in the placebo arm). For those who received RT alone, the dropout rate was less (48 % overall; 52 % in the honey arm and 41 % in the placebo arm). None of these differences were statistically significant.

As many of the dropouts failed to show up for their weekly assessment appointment, there are some missing data, and some subjects attended for their assessments but took very little or none of the study product after the first week. All patients who had at least one mucositis assessment are, however, included in the analysis. The time on study presented in this study is the time from first treatment to last mucositis assessment, irrespective of whether the patient took the study product. All analyses are, therefore, on intention to treat basis. The majority of contactable dropouts reported nausea and the strong taste to be the biggest issues with both products. Two patients in the honey arm reported a burning sensation in the mouth after application, which was not reported from any of the placebo patients. It should be noted that these patients were all experiencing at least moderate–severe background nausea. Two thirds of the patients were receiving emetogenic chemotherapy; the majority was receiving cisplatin.

Primary outcome measure results

Highest RTOG score

The results are shown in Table 6. Comparing the 81 patients who had at least one mucositis assessment, 14 out of 40 (35 %) in the honey arm had worst RTOG score ≥ 3 as compared with 18 out of 41 (44 %) in the placebo arm, but this difference was not statistically significant. When only 64 of those who took the study products for more than 1 week were analyzed, the RTOG score ≥ 3 rates were 36 % in the honey arm and 46 % in the placebo arm. This difference is still not statistically different.

Patients in the honey arm tended to drop out of the study earlier (median, 22 vs. 31 days) so may not have stayed in the study long enough for more severe mucositis to be documented near the end of radiation treatment. However, of the 48 patients who had complete weekly mucositis assessments, the proportion of patients who had a highest RTOG score ≥ 3 was no different between the honey (52 %) and placebo (48 %) arms ($p = 0.7726$).

Table 7 Wilcoxon scores (rank sums) for variable AUC RTOG score by study arm

Study arm	*N*	Sum of scores	Expected under H0	Standard deviation (SD) under H0	Mean score
Honey	32	1,110.0	1,152.0	86.350947	34.687500
Placebo	39	1,446.0	1,404.0	86.350947	37.076923

Average scores were used for ties. Wilcoxon two-sample test normal approximation, $p = 0.6308$

Table 8 Wilcoxon scores (rank sums) for variable AUC WHO scores by study arm

Study arm	*N*	Sum of scores	Expected under H0	SD under H0	Mean score
Honey	31	1,076.50	1,085.0	82.773522	34.725806
Placebo	38	1,338.50	1,330.0	82.773522	35.223684

Average scores were used for ties. Wilcoxon two-sample test, $p=0.9230$

It is possible that the more severe nausea experienced by those who received CRT may have affected compliance sufficiently that any possible benefit was lost. However, of the patients who received radiation alone, 5 out of 21 (24 %) of the honey arm experienced the highest RTOG score ≥ 3 as compared with 5 out of 16 (31 %) of the placebo arm. This small difference was not statistically significant ($p=0.7165$) and did not approximate the level of benefit shown in the first reported study [14]. In the CRT patients, the RTOG score ≥3 rates were 47 % in the honey arm and 52 % in the placebo arm (see Table 6).

Though there were 81 patients with at least one mucositis assessment who were included in the peak mucositis severity analysis, there were 10 patients who only had one mucositis assessment so were unable to be included in the AUC analysis. This analysis was, therefore, carried out on the 71 patients with at least two mucositis assessments. No differences were found between the peak OMAS scores or the peak WHO scores, nor the AUC for any of the three outcome assessment scales (see Tables 7, 8, and 9 and Figs. 2, 3, and 4). No differences were found in quality of life, symptom scores, or sialometry. These data are not presented here in the interests of space constraints, but are available on request. Unfortunately, the presence or absence of oral candidiasis was not recorded in this study.

Discussion

While this study was ongoing, three further reports were published, all showing dramatic differences in mucositis severity comparable with the Malaysian study [14]. In 2008, a randomized study [23] compared saline solution mouth rinse with 20 ml honey from bees fed on thyme and astragale in the Alborz Mountains of Iran. The honey was swished and swallowed three times per day with only 3 out of the 20 honey-treated patients unable to tolerate the treatment. The mean OMAS score in the control group peaked at 28.76 (range, 7.19–16.58) at the end of week 3, compared with a peak in the same week at 11.68 (range, 1.48–1.25) in the honey-treated group.

Later, in 2008, a randomized but uncontrolled study was reported which used 20 ml honey from bees fed primarily on Egyptian clover (*Trifolium alexandrinum*) [24]. The honey was swished and swallowed three times per day as in both of the other studies. All of the honey-treated patients were reportedly able to tolerate the treatment. Only three (15 %) of the honey-treated group were reported to have RTOG ≥3 mucositis as compared with 12 (60 %) in the control group.

In 2010, a single-blinded randomized study used 20 ml honey from bees from the Western Ghat forests compared with lignocaine (lidocaine) gel [25]. The honey was swished for 2 min and then expectorated three times per day, with all honey-treated patients reportedly able to tolerate the treatment. Only one (5 %) of the honey-treated group was reported to have RTOG ≥3 mucositis as compared with 15 (75 %) in the control group.

A recent systematic review and meta-analysis of these studies point out flaws in these studies and recommended further studies be done with more rigorous methodology [26].

A randomized uncontrolled New Zealand study attempting to replicate the original Biswal study (20 ml of honey swished and swallowed three times a day) had to be closed because of poor tolerance to honey [27]. A total of 28 patients were recruited; 10 patients received standard care and 18 patients were given additional manuka honey. The first six patients randomized to the honey arm used undiluted honey and pulled out in the first week because of extreme nausea, vomiting, and stinging sensations in the mouth. The next 12 honey patients used a honey mouthwash (diluted 1:3 in water). Six of these patients completed the trial and four more dropped out after 4 weeks. Eight control patients completed the trial. Though

Table 9 Wilcoxon scores (rank sums) for variable AUC OMAS scale by study arm

Study arm	*N*	Sum of scores	Expected under H0	SD under H0	Mean score
Honey	31	1,058.0	1,085.0	82.820522	34.129032
Placebo	38	1,357.0	1,330.0	82.820522	35.710526

Average scores were used for ties. Wilcoxon two-sample test normal approximation, $p=0.7490$

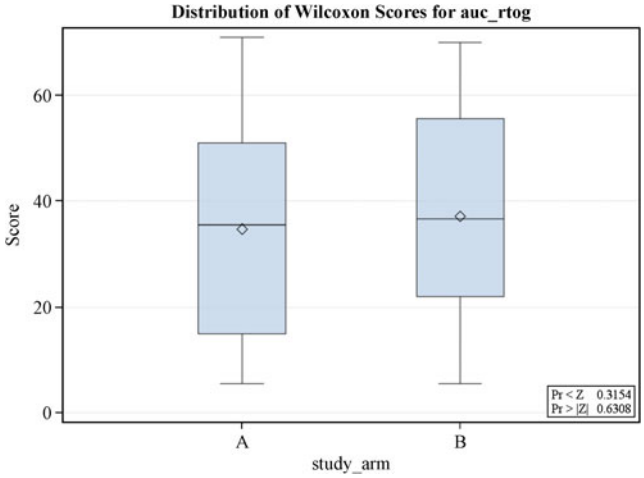

Fig. 2 Distribution of Wilcoxon scores for AUC RTOG scale (*A* honey, *B* placebo)

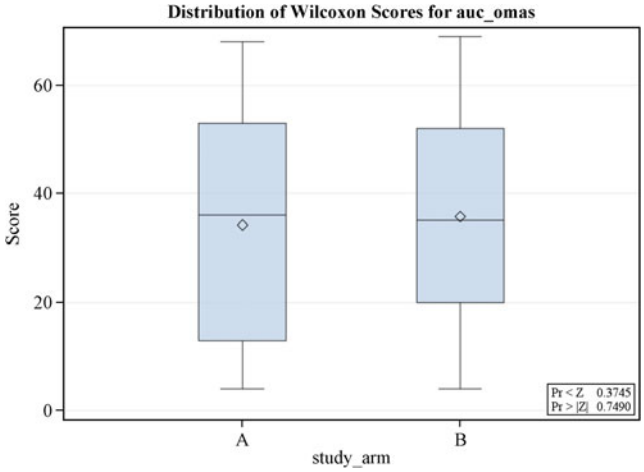

Fig. 4 Distribution of Wilcoxon scores for AUC OMAS scale (*A* honey, *B* placebo)

the numbers were too small for statistical analysis, diluted manuka honey did not decrease the extent and onset of ROM. However, the honey did appear to ameliorate radiation-induced weight loss and increase quality of life in those who did not receive concurrent chemotherapy.

A randomized controlled study undertaken in Manchester, UK, using golden syrup as a control, successfully recruited 131 very similar patients to our study [28]. Their aim was for 20 ml manuka honey or golden syrup to be swished and swallowed four times daily for 6 weeks. Compliance was a problem after the onset of mucositis, which may have affected the findings. However, there was no difference between the two arms of the study, with grade 3 mucositis rates of 80 % in the honey arm and 75 % in the golden syrup arm ($p = 0.64$). The AUC for weekly assessments was also not different ($p = 0.79$).

There are a number of possible reasons why the results in New Zealand, England, and Canada might be different from those obtained in other countries, including differences in the type of honey, study methodology, patient characteristics, assessment tools, and anticancer treatment protocols.

All studies used similar unpasteurized honey, and the positive studies used honey derived from bees feeding on four different types of flowers. Therefore, the source of the honey does not seem to be important. Our study was the only study in which the product was irradiated. Yet, the Manchester and New Zealand studies had similar results to our study. Therefore, it seems unlikely that the irradiation process destroyed any active ingredient.

Unblinding was not a major limitation of our study. The study products were both described as "honey-based gels" and blinding was excellent. The high dropout rate was the same in both arms of our study. One patient had to be taken off the study because he admitted to self-medicating with manuka honey from a health food shop during the study. It is possible that others did so but did not disclose that to the mucositis assessors.

The peak RTOG and WHO scores could have been inadequately sensitive to reveal a clinically significant difference. Anticipating this, we had hoped that the OMAS scale would prove to be more sensitive; however, even this scale did not reveal any significant difference between the two arms. Further analysis of the relationship between the three scales will be presented separately.

The cultures of Canada, New Zealand, and England are similar and have predominantly public health care systems. Honey does not have any special significance in the predominantly Christian religions of the Commonwealth, in contrast to the references to honey's healing powers in the Koran, which may also have affected compliance in the predominantly Muslim countries reporting positive results. Did our patients not follow instructions as diligently as the patients from the other cultures? We believe this to be unlikely, as personal interaction with our patients suggests that they were, on the

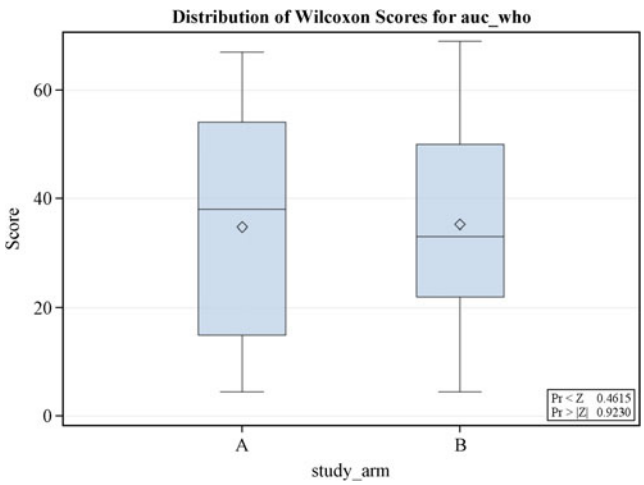

Fig. 3 Distribution of Wilcoxon scores for AUC WHO scale (*A* honey, *B* placebo)

whole, very committed to the study and did try their best to take the products as instructed. Many were enthusiastic about complementary and alternative medicines (CAM). CAM use is increasing in many Western cultures. Access to information from the Internet was actually a problem for us. As mentioned previously, some eligible patients declined to participate because they were already convinced of honey's "healing powers" and did not want to take the chance of being assigned to the placebo arm.

If honey is effective only for mucositis induced by radiation without chemotherapy, the higher than expected proportion of patients receiving chemotherapy in our study could have biased the results away from showing a benefit. However, the rates of mucositis in each arm differed only slightly when those with radiation alone were analyzed separately.

The Manchester study and our study could have missed a useful benefit because of the placebo being actually active. Though we did not do any antimicrobial surveillance tests in our patients, patients in both arms of the Manchester study had a less than expected incidence of oral bacterial infections, suggesting that the osmotic effect of honey and syrup was the primary antimicrobial factor. If microbial load contributes to mucositis severity (as has not been shown in other studies), then the rates of mucositis would have been expected to be less than expected in both arms. Our severe mucositis rates were less than expected based on historical data, but this is probably at least partly due to the high dropout rate, with those experiencing more severe mucositis more likely to drop out. The Manchester study did not find any difference in their patients either.

The low rate of severe mucositis may have been due to selection bias, as people who participate in clinical trials are known to do better in general than unselected patients. The low rate could also be due to the more widespread use of IMRT in the period of the trial as compared to prior studies. We predicted severe (RTOG greater than or equal to grade 3) mucositis in 55 % of those receiving RT alone but found only 24 % in the honey arm and 31 % in the placebo arm. In those receiving chemoradiation, we expected 75 % greater than or equal to grade 3 mucositis but found only 47 % in the honey arm and 52 % in the placebo arm.

Conclusion

This is the second large randomized double-blind placebo-controlled study of honey for radiation mucositis to be reported. Though a few patients liked it, the acceptability of honey overall was very poor, especially in those receiving concurrent chemotherapy. The difference in incidence of maximum mucositis severity of RTOG grade 3 or 4 between the study arms was not statistically significant. The contrast between our results and those of smaller uncontrolled studies is striking and may be a result of methodological differences or because of an active osmotic effect of both honey and placebo.

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Conflict of interest The authors have no conflicts of interest.

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