European Journal of Oncology Nursing 34 (2018) 89–97

Contents lists available at ScienceDirect

European Journal of Oncology Nursing

journal homepage: www.elsevier.com/locate/ejon

The effect of the use of thyme honey in minimizing radiation - induced oral mucositis in head and neck cancer patients: A randomized controlled trial

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ARTICLE INFO

Keywords:
Head and neck cancer
Management
Honey
Radiation-induced mucositis

ABSTRACT

Purpose: Radiation-induced oral mucositis is one of the main side effects during and after the treatment of head and neck cancer patients. The study was designed to provide evidence on the effectiveness of thyme honey on oral mucositis management.

Methods: This was a randomised controlled trial (RCT) with 72 head and neck cancer patients who were divided either to the intervention group (thyme honey rinses) or to the control group (saline rinses). Oral mucositis was assessed according to the Radiation Therapy Oncology Group (RTOC criteria), and assessments were performed weekly starting at the 4th week of the radiotherapy for seven weeks and repeated once 6 months later. Additionally, the Oral Mucositis Weekly Questionnaire (OMWQ) was given at 4th week of radiotherapy, 1 month after the completion of radiotherapy and 6 months later. The ClinicalTrials.gov Identifier for this study is NCT01465308. This paper reports on the findings regarding thyme honey's effectiveness on oral mucositis.

Results: Generalized estimating equations revealed that patients in the intervention group were graded lower in the objective assessment of oral mucositis ($p < 0{,}001$), maintained their body weight ($p < 0{,}001$) and showed an improvement in their global health ($p = 0.001$) compared to the control group. Quality of life of the patients in the same group was also statistically significantly higher than that of the patients of the control group ($p < 0{,}001$).

Conclusion: The study provided evidence on the positive effect of thyme honey on the management of radiation-induced oral mucositis and quality of life in head and neck cancer patients.

1. Introduction

Radiation-induced oral mucositis (OM) is the epithelial damage that may occur on oral, pharyngeal and laryngeal mucosa, as a result of the ionizing radiation exposure mainly between the 2nd and 3rd week of conventional radiotherapy (Radvansky et al., 2013). To this date, radiation-induced OM remains one of the most common side effects of radiotherapy in head and neck (H&N) cancer (Al Jaouni et al., 2017).

OM can be of varying degrees, with more severe OM leading to mouth ulcers, painful dysphagia and consequently to poor quality of life (QoL), but also in discontinuance of the treatment (Mercadante et al., 2015). The duration of the symptoms normally extends over a -6-week period following the start of radiation therapy and resolve within 8 weeks after the completion of treatment (Bensinger et al., 2008). Its severity depends on several factors related to the diagnosis and treatment, the interval between the day of treatment, the radiation daily dose, previous exposure to chemotherapy, concomitant chemotherapy, the characteristics of the patient, oral hygiene and the existence of co-morbidities (Mallick et al., 2016).

The management of OM aims both to relieve the symptoms, but also to minimize any secondary complications (Shueng et al., 2009). As part of a comprehensive management strategy for OM, head and neck cancer patients are taught by the health professionals to implement good oral care and hygiene measures, encouraged to use analgesics, and advised to take high-calorie foods with essential nutrients to speed-up the healing process (Harris et al., 2008).

Furthermore, there are numerous pharmacological and non-pharmacological agents available for the treatment of OM (Kobya and Güdücü, 2016). A number of these agents have been studied and used for OM locally with mixed results. These include sucralfate (Loprinzi

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https://doi.org/10.1016/j.ejon.2018.04.003
Received 11 August 2017; Received in revised form 6 April 2018; Accepted 13 April 2018

et al., 1997; Meredith et al., 1997), antiseptic solutions (Donnelly et al., 2003; Sonis, 2004), the chlorhexidine gluconate (Harris et al., 2008), vitamin E (Koj, 1996) and Vitamin A (Cohen et al., 1997) anti-inflammatory agents, cytokines (Herrstedt, 2000), growth factors (TGF-b, KGF) (Oelmann et al., 2004; Auf dem Keller et al., 2004), prostaglandin E1, E2 (Pastuszak et al., 1998), and various antiseptic mouthwashes (Plevova, 1999). In addition, amifostine, a cytoprotective agent, have been used to treat OM which has shown promising results (Sonis, 2004; Spencer et al., 2005).

Despite the wide range of local and systemic methods used to manage radiation-induced OM, none of the available methods (or combination of pharmaceutical methods) provides an effective, comprehensive and free from secondary side-effects management (Lalla et al., 2011) This has strengthened the need for further investigation of other interventions including complementary and alternative (CAM) interventions for the management of radiotherapy-induced OM.

Honey has been used historically for its medicinal properties. It has been used to heal burns, surgical wounds, and oral infections because of its antibacterial and analgesic agents and epithelialization boosting effect (Alam et al., 2014; Belcher, 2014). The effectiveness of honey on OM might be because of the hygroscopic nature of honey, its viscosity, its acidic pH, which prevents bacteria growth on the mucosa, inhibin (hydrogen peroxide) converted from glucose oxidase and gluconic acid, enzymes which probably are growth factors and tissue nutritive minerals and vitamins that help repair the tissue directly (Molan, 2001; Biswal et al., 2003; Bardy et al., 2008). Furthermore, Vandamme et al. (2013) report that honey improves epithelisation of tissue when used for wound dressing and as a result it improves overall wound healing.

Honey was found to be effective in a small number of studies for the management of OM in head and neck cancer patients undergoing chemoradiation (Biswal et al., 2003; Rashad et al., 2009; Rashad et al. 2009; Khanal et al., 2010; Jayachandran and Balaji, 2012). However, contradicting results are reported elsewhere (Bardy et al., 2012; Parsons et al., 2012; Hawley et al., 2014). Caution is however needed when looking at previous results as in most studies there were significant methodological limitations narrowing the margin for any safe robust conclusions. These included poor methodological design, such as underpowered studies, poorly defined inclusion and exclusion criteria, high drop-out rates and poor adherence to the interventions.

2. Materials and methods

2.1. Aim

The aim of this randomised controlled trial (RCT) was to assess the effect of thyme honey on the grade and duration of treatment-induced OM in head and neck cancer patients.

2.2. Study hypotheses

The trial was designed to test the following hypotheses:

2.2.1. Primary hypothesis

1. Patients in the intervention group will experience lower OM grade compared to the patients in the control group

2.2.2. Secondary hypotheses

1. Patients in the intervention group will lose less weight compared to the patients in the control group
2. Patients in the intervention group will experience less oral problems (i.e. swallowing, drinking, eating, mouth and throat pain) compared to the patients in the control group.
3. Patients in the intervention group will experience better quality of life compared to the patients in the control group.

2.3. Study design – setting

To explore the above hypotheses, a parallel randomised controlled trial with two groups (intervention and control) was undertaken. The study was conducted at the Cyprus Oncology Centre (BOCOC) that provides specialized treatment and care for H&N cancer patients.

2.4. Recruiting, randomization and masking

Consultants in radiation oncology recruited the patients according to pre-determined inclusion and exclusion criteria and obtained their informed consent. Following the decision to participate in the study, baseline measurements were undertaken according to study protocol. Patients were then randomly allocated in one of the two groups. Randomization was achieved by using the envelope method. Patients were asked to choose a sealed envelope that would determine their group. This process was overseen by an external third party.

2.5. Sample size

G Power analysis was performed to calculate the minimum sample size. Seventy-two participants were sufficient to statistically identify a difference of 30% in the prevalence of severe OM (grade 3 and 4) between the Control and Intervention groups with a statistical power 80% and 5% level of significance. The 30% prevalence was chosen as it was the smallest difference [Control group; 15%, Intervention; 45%] observed in the literature (Biswal et al., 2003; Rashad et al., 2009; Rashad et al. 2009; Khanal et al., 2010; Jayachandran and Balaji, 2012).

2.6. Participants (inclusion and exclusion criteria)

Patients with H&N cancer diagnosis (squamous cell carcinoma) with primary and non-metastatic cancer referred for Intensity Modulated Radiation Therapy (IMRT) at a dose between 50 and 60Gy in the oral cavity were included in this study. The inclusion criteria were: a) patients with OM degree 1 or above based on the RTOG (Radiation Therapy Oncology Group) criteria, b) age > 18 years old, c) three weeks preceded radiotherapy, d) able to complete the study assessments and e) willing to participate in the study. The exclusion criteria were: a) patients with diabetes mellitus, b) known allergies to thyme honey, c) presence of OM prior the onset of this study e) radiotherapy within the last 6 months prior to this study.

2.7. Intervention and procedures

In the intervention group, thyme honey was given to the patients as oral rinses based on a previously developed protocol (Biswal et al., 2003). Patients were advised to dilute 20 ml of thyme honey in 100 ml of purified water making gargles in the oral cavity (15 min before and after the radiotherapy session and 6 h later), three times a day for seven weeks (starting from the first day of the 4th week of radiotherapy) (Fig. 1). The decision to use this time-point as one of the study's measurements (in relation to time) was informed by the relevant literature. For example, Elad and Zadik (2016), found that extensive painful oral mucositis lesions developed in all patients during the course of radiotherapy, with ulcers remaining for 5–24 months after completion of therapy. This time-point as a follow-up for the patients in both groups helped the researchers to test the longer effects of the intervention.

Detailed oral and written instructions were given to the patients enable them to faithfully follow the administration protocol. Patients in the control group used normal saline oral rinses instead of thyme honey in the same quantity and periods of time. Furthermore, patients in both groups were instructed not to swallow the oral rinses. All the patients who participated in the study were informed by their consultants of the oral hygiene including the use of a soft tooth brush and a high fluoride toothpaste. Furthermore they were given both written and verbal