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Review article

The effectiveness of honey for the management of radiotherapy-induced oral mucositis in head and neck cancer patients: A systematic review of clinical trials

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Abstract

Aim: To evaluate the effectiveness of honey in the management of oral mucositis in head and neck cancer patients undergoing radiotherapy.
Methods: The review of the literature was based on a keyword strategy and pre-determined inclusion and exclusion criteria. The keywords "head and neck cancer", "radiotherapy", "oral mucositis", "controlled trial" and "honey" were used as search terms in the EMBASE, CINAHL, COCHRANE and PUBMED databases. The citation and reference list of the eligible articles were also screened for potentially relevant articles. The methodological quality of the selected trials was assessed by the JADAD scale.
Results: In total, 5 studies met the criteria and were included in the systematic review. Three studies assessed the effectiveness of honey against other products including golden syrup, lignocaine and saline and two studies assessed the effectiveness of honey against standard treatment regimes. Four out of the five studies demonstrated significant reduction in the mucositis levels and one study reported that honey had no statistical association with less severe mucositis. Methodologically the quality of most studies was moderate due to the small sample size, which might impact upon the significance of the findings.
Conclusions: Although honey appears to be a simple, affordable, available and cost-effective treatment for the management of radiation-induced oral mucositis, there is a need for further multi-centre randomized trials to validate these findings.

Keywords: Clinical trials; Honey; Oral mucositis; Radiation therapy; Head and neck cancer

Introduction

An estimated 36,500 new cases of and 7900 deaths from oral cavity and pharyngeal cancers occurred in 2010 in the United States [1]. Squamous cell carcinoma or a variant is the histologic type in more than 90% of these tumours [2,3]. The three main kinds of treatment that may be given independently or in combination, for head and neck cancers include surgery, chemotherapy and radiation therapy (RT). The treatment plan for an individual patient depends on a number of factors including the location of the tumour, the stage and the pathologic findings. These factors consecutively guide the appropriate radiation protocol, chemotherapy regime or surgical procedure to be followed [4]. Single-modality treatment with surgery or radiotherapy is generally recommended for 30–40% of stage I–II head and neck cancer patients [5]. In addition to its desired effect on cancer cells, radiation therapy often causes acute toxicities although most of them are temporary. Most side effects occur towards the middle and the end of the course of treatment and continue during the first couple of weeks after the treatment has finished. The effects can be mild or severe, depending on the dose of RT and the length of the treatment. Oral mucositis is one of the most

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common, severe and persistent side effects that patients with head and neck cancer confronted during and after radiotherapy.

Molecular and cell biology in oral mucositis is a multistep process. Sonis [6] has described a five phase model to characterize the theory for the pathogenesis of oral mucositis. These phases include initiation, signalling, amplification, ulceration and healing [6]. According to this theory, reactive oxygen species generated by exposure to radiation therapy or chemotherapy result in DNA strand breaks and that causes damage to the cells, tissues and blood vessels. These damages activate transcription factors which cause increased production of pro-inflammatory cytokines like interleukin that lead to tissue injury and apoptosis. The cytokines cause further tissue damage which amplifies the signalling cascade that lead to ulceration and inflammation. A signal send by the submucosal tissue initiates the healing process which in turn stimulates epithelial proliferation and cellular differentiation restoring the lining of the oral cavity [6].

The development of oral mucositis is an expected accompaniment of radiation therapy applied to the head and neck regions. Severe radiation mucositis leads to ulceration and painful dysphagia that can negatively influence the quality of life and force the discontinuation of treatment. At least 50% of patients will experience some grade of oral mucositis as well as grade 3 mucositis when 66–70 Gy radiation are delivered to large mucosal surfaces in 6–7 weeks with 1.8–2 Gy per fraction [7].

A variety of treatments are used for the prevention and the management of oral mucositis and the choice of the treatment depends on the patient's condition and needs. The most usual categories of these agents include topical cytoprotective agents (e.g. sucralfate), anti-inflammatory agents (e.g. benzydamine hydrochloride), antibacterial agents (e.g. chlorhexidine) topical or systemic anti-oxidants (e.g. amifostine, vit. E) and sialogogues [8–10]. Cryotherapy and low-level laser therapy found to be helpful in reducing the severity of chemotherapy and radiation-induced oral mucositis [11,12]. Keratinocyte growth factor (KGF-1, palifermin), G-CSF and GM-CSF factors and glutamine (nonessential amino acid) are some of the therapies which have recently been evaluated for preventing and managing oral mucositis [13–15]. Despite the availability of treatment options for oral mucositis, these do not seem to provide an effective and comprehensive management method [16].

In the light of the ineffectiveness of these conventional means, health-care professionals and the public alike turned to complementary and alternative medicine (CAM) in order to find ways to better manage oral mucositis. However, a dilemma emerged regarding the use of such methods (i.e. honey) due to the lack of consistent scientific evidence in relation to their efficacy and safety. Nevertheless, an increasing number of cancer populations use CAM as adjunct therapies whether prescribed or not [17,18]. Despite the increased attention on such methods in different cancer populations there has been a disproportional study for their use in head and neck cancer patients [19]. The available preceding studies emphasized the management of various treatments related side-effects experienced by head and neck cancer patients through the use of CAM [20–23]. Among these treatments that have been explored is that of natural honey.

Some studies refer to honey as one of the traditional medicines that have beneficial properties to health [24,25] including its ability to facilitate the healing process. Molan, stressed that honey facilitates an increase in lymphocytes and phagocytes and aids monocytes to release cytokines and interleukins, thus stimulating the healing process [24]. Hence there is a reasonable justification that honey can enhance phase 3 of oral mucositis' pathogenesis which involves signalling and amplification.

Honey is acidic with a pH ranging from 3.2 to 4.5, which serves to inhibit the growth of pathogens as the majority thrives at a pH between 7.2 and 7.4 [24,25]. High sugar content of honey draws water from the wound, reducing the availability of water to the pathogens, which further impedes microbial growth [26]. It also contains the enzyme glucose-oxidase that stimulates the release of hydrogen peroxide after contact with body tissue, which has an antiseptic effect [27,28] and within some types of honey there are phytochemicals which are known to have bactericidal properties [28,29]. These properties may help phase 4 (ulceration and inflammation) of the biologic process of mucositis and thus minimize more severe mucositis and colonization by oral bacteria and the risk of sepsis.

Honey contains numerous compounds such as organic acids, proteins, aminoacids, minerals, polyphenols, vitamins and aroma compounds [29] and its composition depends greatly on the botanical origin [30]. Despite the fact that the contribution of honey to the recommended daily intake is small, it can help head and neck cancer patients undergoing radiation therapy and chemotherapy who suffer from malnutrition and increased weight loss [31]. Studies have also shown that honey applied to wounds reduced and relieved pain, a symptom that accompanies patients with oral mucositis [21,31,32].

Although several studies explored the effectiveness of honey in different side-effects, there is a need for further research looking at the use of honey explicitly for the management of radiation-induced oral mucositis. This is strengthened by the fact that to date, there is only one systematic review by Bardy et al. [31] exploring the use of honey and its potential value within oncology care, but it does not fully explore its effectiveness in radiotherapy induced-oral mucositis in head and neck cancer patients.

The aim of this study is to retrieve and review the available Randomized Control Trials (RCTs) that have a clear focus on the effectiveness of honey in the management of radiotherapy induced-oral mucositis in head and neck cancer patients.

Materials and methods

EMBASE, CINAHL, COCHRANE and PUBMED electronic databases were thoroughly searched from 1977 to date. The search was undertaken from January to March 2012 in order to identify the articles that met the inclusion and exclusion criteria.

The search strategy was identical for each of these electronic databases and was undertaken with the use of the following key