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Meta-Analysis
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Effects of honey use on the management of radio/chemotherapy-induced mucositis: a meta-analysis of randomized controlled trials

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Abstract. This meta-analysis aimed to assess the prophylactic effects of honey use on the management of radio/chemotherapy-induced mucositis. PubMed, Cochrane Library, Science Direct, China National Knowledge Infrastructure (CNKI), VIP (Chinese scientific journal database), and China Biology Medicine (CBM) were searched for relevant articles without language restriction. Two reviewers searched and evaluated the related studies independently. Statistical analyses were performed using Stata 11.0, calculating the pooled risk ratio (RR) with the corresponding 95% confidence interval (CI). Begg's funnel plot was used together with Egger's test to detect publication bias. A total of seven randomized controlled trials were finally included. Quality assessment showed one article to have a low risk of bias, two to have a moderate risk, and four to have a high risk. Meta-analysis showed that, compared with blank control, honey treatment could reduce the incidence of oral mucositis after radio/chemotherapy (RR 0.35, 95% CI 0.18–0.70, $P = 0.003$). No meta-analysis was applied for honey vs. lidocaine or honey vs. golden syrup. The sensitivity analysis showed no significant change when any one study was excluded. No obvious publication bias (honey vs. blank control) was detected. In conclusion, honey can effectively reduce the incidence of radio/chemotherapy-induced oral mucositis; however, further multi-centre randomized controlled trials are needed to support the current evidence.

Key words: honey; radio/chemotherapy; mucositis; meta-analysis.

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Head and neck cancer, including cancer of the oral cavity, oropharynx, hypopharynx, or larynx, is the sixth leading cause of cancer-related death worldwide.[1,2] It is recognized as a public health problem that affects the physical and mental health of people all over the world.[3,4] Currently, the main method for the treatment of head and neck cancer is surgical resection supplemented by radiation therapy and/or chemotherapy. For the early stage of disease, surgical resection is potentially effective, while for the advanced stage, the addition of radiotherapy, chemotherapy, or the combined use of radiotherapy and chemotherapy (radio/chemotherapy) is required and considered standard treatment.[5]

Radio/chemotherapy treatment is nonspecific for human tissues. It does not correctly distinguish normal human cells from malignant proliferating tumour cells, and thus interferes with the proliferation and differentiation of both cell types equally, killing them.[6] Oral mucosal cells have a high frequency of proliferation and self-renewal, and are susceptible to the impact of radio/chemotherapy, which leads to oral mucositis symptoms of pain, erythema, and ulcers, etc.[7] In the process, patient compliance may be affected significantly.

A number of biological agents have been applied to prevent and treat patients with oral mucositis resulting from radio/chemotherapy, including granulocyte/macrophage colony-stimulating factor,[8] the prostaglandin E analogue misoprostol,[9] corticosteroids,[10] and amifostine.[11] The response to these has been variable, with reported problems including a lack of efficacy, inconvenience in use, and potential toxicity.[12–14]

Honey is produced by bees from flower nectar.[15] In recent years, there has been a resurgence of interest in the use of honey for the management of radio/chemotherapy-induced mucositis. In 2003, Biswal et al. conducted a randomized controlled trial to study the effects of honey use on the management of radio/chemotherapy-induced mucositis.[16] Since then, numerous associated studies have been published, with conflicting results reported. Some have shown that honey has a significant impact on the severity of radio/chemotherapy-induced mucositis,[17–20] while others have not detected any efficacy.[21]

For clinical doctors to gain a better understanding of the therapeutic effects of honey, it is necessary to critically and systematically review the published results of randomized clinical trials and to perform a comprehensive meta-analysis of these trials.

Materials and methods

Search methods and key words

A comprehensive search was performed in PubMed, the Cochrane Library, Elsevier Science Direct, China National Knowledge Infrastructure (CNKI), VIP database (Chinese scientific journal database), and China Biology Medicine (CBM) to collect relevant published studies on the use of honey for the prevention and treatment of radio/chemotherapy-induced mucositis. Furthermore, a manual search and screening of the references reported in the studies identified was also performed. The following search terms were used: 'honey', 'oral mucositis', 'mucositis', 'randomised', and 'randomized'. An upper date limit of 30 September 2015 was applied; there was no lower date limit. There was no language restriction. The search strategy used in PubMed was as follows:

#1 honey [Title/Abstract];
#2 oral mucositis [Title/Abstract];
#3 mucositis [Title/Abstract];
#4 (#2 OR #3);
#5 randomised [Title/Abstract];
#6 randomized [Title/Abstract];
#7 (#5 OR #6);
#8 (#1 AND #4 AND #7).

Inclusion and exclusion criteria

Inclusion criteria were the following: (1) randomized controlled trials, whether or not blinding methods were applied; (2) head and neck cancer patients undergoing radiotherapy and/or chemotherapy; (3) test group receiving honey treatment and control group receiving no other treatment (blank control) or receiving another single factor intervention (lidocaine or golden syrup); other treatments or other potential factors had to be consistent between the two groups; (4) outcome measure being the incidence of oral mucositis within 1 week after radio/chemotherapy (World Health Organization (WHO),[22] Radiation Therapy Oncology Group (RTOG),[23] or Oral Mucositis Assessment (OMA)[24] scale scores of oral mucositis $\geq$3 were defined as clinical symptoms).

Exclusion criteria were as follows: (1) review articles or letters to the editor; (2) animal or laboratory studies; (3) case reports; (4) technical reports.

Data extraction

The data from all eligible articles were extracted independently by two reviews (JLX and ZHS) using predefined data abstraction forms. The following information was extracted from each study (when available): first author, publication year, study design, single-centre or multi-centre study, population characteristics, intervention characteristics, the source of the honey, the administration of honey, assessment scale types, and mucositis scores.

Assessment of the methodological quality

Two reviewers (JLX and ZHS) evaluated the quality of all included studies independently, according to the risk of bias assessment scale for randomized controlled trials recommended in the Cochrane handbook for systematic reviews, and these were cross-checked. Disagreements between the two reviewers were resolved by consensus with a third reviewer (RX). The classification of the risk of bias potential for each study was based on the following criteria: random sequence generation, allocation concealment, blinding of participants, blinding of implementers, incomplete outcome data handled appropriately, absence of selective reporting, and absence of other sources of bias. If all assessment items are reported as 'yes', the study is judged to be at low risk of bias. If one or more items are reported as 'unclear', the study is considered to be at moderate risk of bias. If one or more items are reported as 'no', the study is regarded as being at high risk of bias.

Statistical analysis

To evaluate the prophylactic effect of honey use on the management of radio/chemotherapy-induced mucositis, a pooled risk ratio (RR) with the 95% confidence interval (CI) was calculated. All effect sizes and 95% CI were calculated on the basis of fixed- or random-effects models. A test of heterogeneity of combined RRs was carried out using Cochran's Q test and Higgins's I^2 statistic. Heterogeneity was defined as $P < 0.05$ or $I^2 > 50\%$. If there was no statistical difference for heterogeneity ($P > 0.05$ or $I^2 \leq 50\%$), a fixed-effects model was to be used to analyse the data (the Mantel–Haenszel method); in the opposite case, a random-effects model was to be applied (the DerSimonian–Laird method). Publication bias among the studies included was evaluated using Egger's linear regression test and Begg's funnel plot.[25] In the case of publication bias, the funnel plot will be asymmetric, or the P-value will be <0.05 by Egger's