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A double blind randomised placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children

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KEYWORDS
Propolis;
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Chemotherapy;
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Summary
Objectives: Chemotherapy-induced oral mucositis (OM) is a debilitating side effect. In addition to standard therapy, patients often use complementary and alternative medicine to treat OM.
Design: Double blind randomised placebo controlled study assessing propolis (bee glue) efficacy for chemotherapy-induced severe OM treatment.
Setting: University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia.
Interventions: Paediatric patients undergoing chemotherapy were randomly assigned to propolis ($n = 19$) or placebo groups ($n = 21$). Patients were introduced to a unified oral care protocol and asked to apply propolis or placebo to vestibular mucosa twice daily. Oral mucosa was assessed with the Oral Assessment Guide (OAG) twice a week when the patients were in hospital. Patients were followed for the period of the chemotherapy or for the first 6 months of the chemotherapy. An OAG score of 3 was considered to be severe OM and analysed.
Main outcome measurements: Three dependent variables (a) OM episode frequency, (b) mean number of assessment visits, at which an OAG 3 score was noted, expressing mean OM duration, (c) mean number of OAG 3 scores expressing mean OM severity) were reduced to a single variable using principal component analysis. A new variable (FDS) was used as the dependent variable in ANCOVA model analysis to show the differences between study groups.
Results: Severe OM was seen in 42% and 48% of patients in the propolis and placebo group, respectively. FDS was not statistically significant between study groups ($p = 0.59$).
Conclusions: According to our study results, propolis cannot be recommended for severe OM treatment.

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Introduction

Oral mucositis (OM) is a term to describe an oral mucosa inflammation as a chemotherapy side effect. Clinical features combine erythema, oedema and sensitivity, followed by painful ulceration and mucosal bleeding. Patients with severe OM are unable to eat, speak or swallow due to pain.[1] The OM prevalence in children with cancer is 52—81%.[2,3] Many strategies and drugs have been tested to treat OM,[4] but none is widely accepted and used.[5] The limited efficacy of conventional medical treatment for OM is why more and more paediatric oncology patients are using complementary and alternative medicine (CAM) to alleviate the side effects of conventional cancer therapy.[6] In Turkish research, paediatric cancer patients used CAM in 73.3% of cases, most often honey.[7] Recent scientific evidence suggests that phenolic compounds of honeybee products, such as honey, royal jelly and propolis, for the most part exert biological properties, including anti-inflammatory, antioxidant and antimicrobial.[8,9] However, it was noted that our paediatric cancer patients have frequently used propolis to treat OM, using an over the counter propolis product that is widely available and used as a supplementary dietary product, with a presumed effect on inflammation and healing. Propolis is a resinous material collected by bees from various plant sources and mixed with the bee's salivary enzymes and beeswax. Bees use it to repair the hive walls and to protect the colony from disease.[10] Processed propolis, most often dissolved in 70% or 95% ethyl alcohol, has long been used in folk medicine, including for treating oral ulcers.[11,12]

An anti-inflammatory action of propolis on the oral mucosa has been noted in denture stomatitis treatment,[13] recurrent aphtosous stomatitis[14] and eosinophilic ulcer treatment.[15] The protective effect of propolis has been proven against oxidative stress induced by the anticancer drugs doxorubicin and vinblastin in rats.[16] An antibacterial, antifungal and antiviral action of propolis has been shown for Viridans streptococci,[17] Candida albicans[18] and Herpes simplex virus,[19] which commonly cause secondary infection in chemotherapy treated patients.[20,21]

Limited and poor scientific data on the efficacy of CAM in oncology and reports of potential interactions with conventional treatments[22] puts health care workers in a predicament about what to advise patients about the use of CAM.[23] Since we could not find any data on propolis usage in OM treatment, we designed the study to assess the efficacy of propolis versus placebo for the treatment of chemotherapy-induced OM.

Materials and methods

The study was approved by the Slovenian National Medical Ethics Committee. Informed written consent was obtained from the parents or caregivers. This study was registered with ISRCTN47055000 number.

Subjects and study design

Eligible subjects were paediatric patients, aged 1—19 years, who had been diagnosed with cancer and had started chemotherapy in the Division of Oncology and Haematology, University Children's Hospital, Medical Centre Ljubljana. The exclusion criteria were (a) allergy to propolis and (b) pre-diagnosed oral disease or therapy for oral disease. Patients were consecutively included and were randomly assigned to propolis or placebo groups by means of a draw. The investigating dentist, patients and nurses giving OM treatment were masked to the treatment group.

Intervention

The oral care protocol consisted of teeth brushing and propolis or placebo application. Instructions were given to the parents and the patients how to brush teeth twice daily, using a soft toothbrush and fluoride toothpaste, which were provided to them free of charge.

In the case of severe mucositis or minimised function (talking, swallowing or salivation), applications were instructed of propolis or placebo to the ulcer and to vestibular mucosa in the morning and evening using a Micro tip applicator (Intel Dental, Ontario, California, USA) until the ulcer was healed and the function was renewed. An average of 0.38 g of propolis or placebo was used for each application. Morning and evening applications were advocated to ensure clinical blinding, since the investigating dentist visited patients in the afternoon. Patients were provided with or propolis mixture or placebo at the beginning of each new chemotherapy cycle according to the allocation, and they were not allowed to buy or obtain the propolis for themselves. Each patient was given an information and instruction folder to reinforce cooperation and help them to remember the protocol. A protocol follow-up and reports on side effects of the preparations were assessed by a questionnaire.

Propolis testing and placebo

Propolis and placebo samples were packed in identical 15 ml dark marked bottles, which were supplied by Medex d.o.o., Ljubljana, Slovenia. The identifying key of the bottles marking was not revealed until the end of the study.

The origin of the raw propolis, collected in 2006, was China. The propolis was ground and 70% ethanolic extract was prepared. This concentration of propolis was used for its thickness and stickiness, in order to minimise the wash out effect of salivation.

The chemical composition of the propolis was investigated using reversed-phase high performance liquid chromatography (RP-HPLC), with a chromatograph equipped with a Puropher Star RP-18 endcapped column (column size 4.6 mm $\times$ 150 mm; particle size, 5 μm) and VWD detector (G1314A, Agilent 1100 series, Agilent Technologies, Inc., Santa Clara, CA, USA). The extract was adequately diluted and filtered with a 0.45 μm filter (Sartorius Stedim Biotech S.A., Aubagne Cedex, France) prior to 10 μl being injected into the HPLC system. The column was eluted by using a linear gradient of 1% formic acid (solvent A) and acetonitrile (solvent B), starting with 30% B and increasing to 65% B (30 min) and decreasing to 30% B (40 min), with a solvent flow rate of 1 ml/min. Chromatograms were recorded at 290 nm. The following authentic standards of phenolic