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Mucoadhesive Propolis Gel for Prevention of Radiation-Induced Oral Mucositis

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Abstract: The objective of this phase II study was to determine the effectiveness of a mucoadhesive propolis gel in the prevention of radiation-induced oral mucositis. Twenty-four patients who were selected to undergo radiation therapy for oral cancer were included in this open-label trial. They were advised to use a mucoadhesive gel containing propolis 5,0% w/v three times a day starting one day before the course of radiation therapy and concluding after 2 weeks of radiation therapy. A weekly follow-up for evaluation of food intake, pain and grading of mucositis was performed. In order to confirm the absence of Candida-related mucositis in patients who developed mucositis, it was performed exfoliative cytology of buccal mucosa, palate and tongue and the material for Candifast® Candida species identification. At the end of the study was made the compliance of patients, quality, appreciation and acceptance of product evaluation. Twenty patients did not develop mucositis, two patients developed grade 1 mucositis and two patients developed grade 2 mucositis. None of the patients discontinued food intake and no pain was observed during the study. Candidosis was not detected in any patient. Mucoadhesive propolis gel could be considered as a potential topical medication for preventing radiation-induced oral mucositis. However, comparative phase III study with larger number of patients should be done for confirmation of the efficacy of the product.

Keywords: Head and neck cancer, mucoadhesive gel, oral mucositis, propolis, radiotherapy.

INTRODUCTION

Surgery and radiation therapy have been the standard treatment modalities employed in oral cancer with a high rate of cure [1]. It is of great concern that the majority of patients with oral cancer are at late stage of the disease and thus in a non-operable condition. Hence, radiation treatment becomes the only treatment option for several patients [2].

Mucosal injury remains an undesirable, painful, and expensive side effect of radiation therapy [1,3]. Approximately 80% of patients receiving radiation therapy for head and neck cancer develop mucositis [4]. Rates of hospitalization due to mucositis are reported to be 16% overall [5].

Current management of oral mucositis is mostly supportive care and includes good oral hygiene, avoiding irritating or abrasive substances, use of oral rinses, topical anesthetic agents, and systemic analgesics. New guidelines are suggesting Palifermin, which is the first active mucositis drug, as well as Amifostine for radiation protection and cryotherapy for symptoms related to high-dose Melphalan therapy [1,6].

Natural products produced by bees *Appis mellifera* have been studied by several researchers worldwide [7,8]. Propolis is extensively used in foods and beverages considering its potential benefits for health [8-10]. It contains more than 300 natural compounds such as polyphenols, phenolic aldehydes, sequiterpene-quinones, coumarins, amino acids, steroids and inorganic compounds. Propolis exhibits a broad spectrum of biological and pharmacological properties such as anti-microbial, antioxidant, anti-inflammatory, immunomodulatory, antitumor, anticancer, antiulcer, hepatoprotective, cardio-protective, and neuroprotective actions [11-13]. The chemical composition and beneficial properties of propolis vary greatly depending on the phytogeographical areas, seasonal collection time, and botanical source [14].

In Brazil and in several countries of the world, propolis has been used by the population for treatment of various diseases of the mouth [15-17]. However, due to lack of clinical studies that prove the propolis efficacy and acceptance of the product as a medicinal scientifically by

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population, dentists not prescribe its use. This causes people to use random products containing the propolis [18]. So, it is necessary to ascertain the adherence, acceptability and genuine opinion of patients regarding product containing propolis even though there is not contra-indication evident. [19,20]. In this phase II clinical study we verified the effectiveness of a Brazilian green propolis mucoadhesive gel in preventing oral mucositis in patients irradiated in the head and neck region and also checked the product acceptability and adherence of patients to treatment.

METHODS

Study Design and Patients

This interventional follow-up phase II study [21-23] was conducted at the Irradiated Head and Neck Patient Clinic, from the School of Dentistry of Federal University of Minas Gerais -UFMG (Belo Horizonte, Brazil). The study was approved by the Ethics Committee on Human Research (COEP / UFMG) number 0249.0.203.000-10) and all patients signed informed consent prior to participation.

Subjects were selected in an open basis based on the following criteria: histopathologically confirmed cases of oral squamous cell carcinoma; indication of head and neck radiation therapy. Exclusion criteria included: patients continuing or not willing to quit smoking or alcohol intake; patients with indication of palliative doses of radiation therapy; previous history of radiation therapy or chemotherapy; history of allergy or any reaction to propolis or to the formula constituents.

A total number of 33 patients were initially enrolled in the study. All patients were advised about smoking cessation and alcohol abstinence. Detailed extra oral and intra oral examination for signs and symptoms of radiation therapy-induced oral mucositis was performed. Patients received 180 cGy/fraction, 5 fractions weekly, 30–35 fractions within 5-7 weeks). Flow diagram about the clinical trial design study is shown in Fig. **1**.

Mucoadhesive Gel Formulation and Prescription

The mucoadhesive gel was produced by Nectar Farmaceutica Ltda (Belo Horizonte, Brazil), according to its own proprietary formulation and standards required by the National Brazilian Sanitary Authority (ANVISA working license MS 0.48631.1), under International ISO 9001 and GMP Certificates. It's main chemical components were identified by high performance liquid chromatography (HPLC) and reverse phase, as described elsewhere [24,25] (Table **1**). The final composition included Brazilian green propolis, purified water, polysorbate 20, propylene glycol and hydroxypropyl methylcellulose. The final concentration of 5% is justified by the *in vitro* experiments against microorganisms and previous clinical trials studies (Pereira *et al*., 2011). Patients were instructed to apply a portion equivalent to a coffee spoon (10 g) three times a day, starting 24h before the first session and during the whole period of radiation therapy. It was advised to apply the product on the tongue and then spread over the oral mucosa. Swallowing the gel was allowed. Patients with difficulties in moving their tongue were advised to apply the gel using a swab or with their finger using latex gloves. Patients were encouraged to apply the gel every eight hours during radiotherapy treatment.

Grading for Mucositis

The degree evaluation of radiation-induced oral mucositis was based on the World Health Organization classification: Grade 0 - no change; Grade 1 - soreness/erythema; Grade 2 - erythema and ulcers; Grade 3 - ulcers (only liquid diet); Grade 4 – food intake not possible. Weekly follow-up was

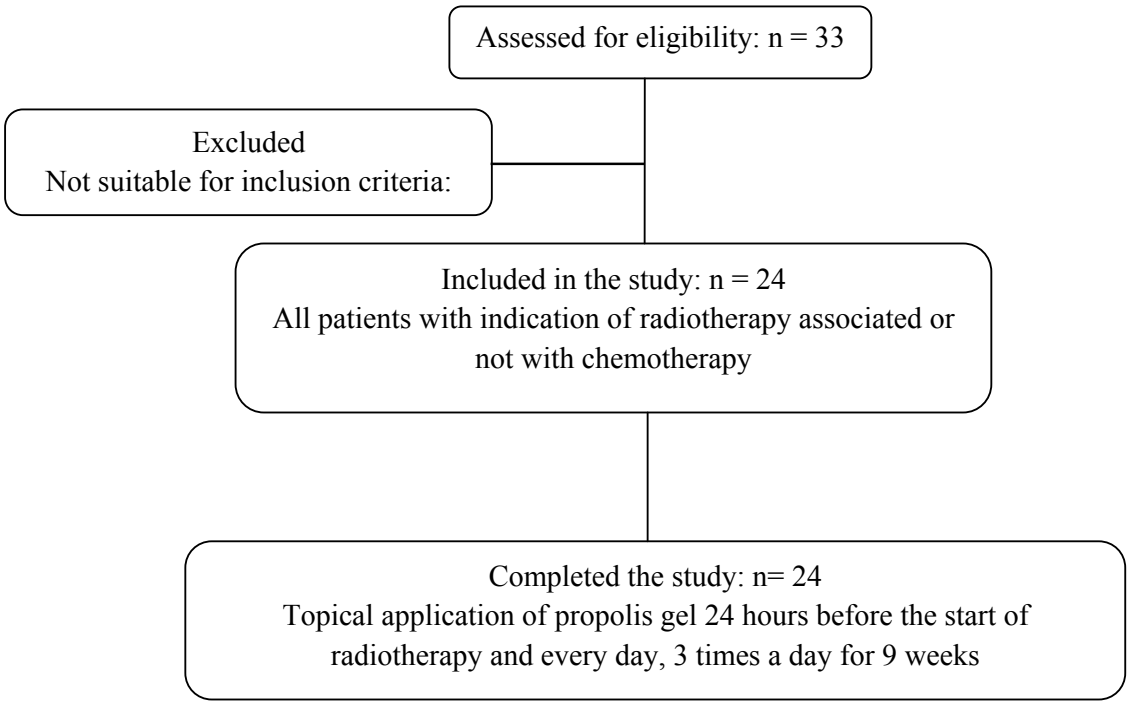

Fig. (1). Flow diagram about the clinical trial design study.

Table 1. Flavonoids and other chemical constituents of Brazilian green propolis from *Baccharis dracunculifolia* [24,25].

Compounds	Contents (mg/g)
Cumarinic acid	3.56
Cinamic acid	1.66
Quercetin	1.38
Kaempferol	1.77
Isoramnetin	0.91
Sakuranetin	5,57
Pinobanksin-3-acetate	13. 92
Crysin	3.51
Galangin	9.75
Kaempferide	11.60
Artepillin C	82.96

implemented for evaluation of mucositis, food intake, and pain (visual analogue scale). Acute exacerbation of signs and symptoms was also monitored during treatment.

Candidosis Evaluation

In order to confirm the absence of Candida-related mucositis in patients who developed mucositis, it was performed exfoliative cytology of buccal mucosa, palate and tongue. Material collected through cytology was seeded on Sabouraud dextrose agar (Difco, USA) containing 1% chloramphenicol for the inhibition of bacterial contaminants. Then they were left at 37°C for 48 hours. If there was growth of these colonies would be used for biochemical tests for identification of Candida species using the kit Candifast® (International Microbio- France).

Evaluation of the Acceptability of the Product

At the end of the ninth week of using mucoadhesive propolis gel all patients were evaluated and answered a questionnaire about the product. The responses were recorded in own document and interpreted through percentage (%). Those items that have reached acceptance equal to or above 80% (> 80%) were considered positive. This evaluation was made considering the methodology used by Cheng [26] and Pereira *et al.* [27].

STATISTICAL ANALYSIS

For the case of a single study group, the statistical analysis of the data collected was performed subjectively by comparison of the percentages of the numbers of patients involved [26,27].

RESULTS

Patients Demographic Characteristics

This study started with the enrollment of 33 patients, but 9 of them died during the course of radiation therapy, making a total of 24 evaluated patients. Subjects consisted of adult patients, 19 men and 5 women, with an age range from 38 to 72 years (mean ± 56.9 years).

MUCOSITIS PREVENTION

The mucosal changes and the effectiveness of mucoadhesive propolis gel for preventing radiation-induced oral mucositis were evaluated weekly. Twenty patients (83,33%) did not develop radiation-induced oral mucositis. Two patients (8,33%) developed grade 1 mucositis from the 4th to 8th weeks, while 2 patients (8.33%) had mucositis grade 2 from the 6th week with regression to grade 1 after the 8th week. Patients did not report pain during the use of the product. Patients with grade 2 mucositis complained of oral discomfort when eating solid foods, but it was not considered as pain. Candidosis was not observed in any patient during the use of mucoadhesive propolis gel.

Candidosis Evaluation

Yeast colonies were not observed in smears samples seeded in Sabouraud agar, not being possible to identify species of Candida.

Evaluation of the Acceptability of the Product

At the end of nine weeks of product use all 24 patients responded to the questionnaire, and a number above ≥ 80%

Table 2. Evaluation of the product (propolis gel) at the end of treatment through interviews of patients.

	Item Rated																		
	Odor			Flavor			Color			Consistency			Application Difficulty		Satisfaction With Outcome			Indication of Product	
	EX	Good	Bad	EX	Good	Bad	EX	Good	Bad	EX	Good	Bad	Not Difficulty	Difficulty	EX	Good	Bad	Yes	Not
Number of patients	11	9	4	9	12	3	24	-	-	24	-	-	24	-	12	12	-	24	-
Percent	45,8	37,5	16,6	37,5	50,0	12,5	100	-	-	100	-	-	100	-	50	50	-	100	-

Legend: EX = excelent.

(n = 19.2) demonstrated that accept and recommend the use of the product. Patients were questioned about flavor, odor, consistency, color and difficulty of use. As for the flavor, 9 (37,5%) patients rated as excellent, 12 (50.0%) as good, and 3 (12,5%) as bad. Considering the odor, 11 (45.83%) evaluated it as excellent, 9 (37.57%) as good, and 4 (16,66%) as poor or bad (Table **2**). Patients did not complain about consistency, color and difficulty of use. All patients were unanimous in reporting that they would recommend this treatment to others. Twelve patients (50%) evaluated it as excellent and 12 (50.00%) as good. Patients with mucositis grades 1 and 2 stated that there was an initial burning sensation which was immediately followed by relief. The patients' reports indicated that sleeping with the gel inside the oral cavity was essential for the good results observed.

DISCUSSIONS

Natural products produced by bees Appis mellifera have been studied by several researchers [18,25,26] for different purposes showing efficacy in results and being well accepted by patients [8,9,14].

Phase II trials are generally small-scale studies, and may include one or more experimental treatments with or without a control. A common feature is that the results primarily determine the course of further clinical evaluation of a treatment rather than providing definitive evidence of treatment efficacy. This means that there is more flexibility available in the design and analysis of such studies than in phase III trials. In addition, these studies try to evaluate the acceptance of the new tested product by patients [21].

This study evaluated the preventive action of a mucoadhesive gel containing 5% of Brazilian green propolis for radiation-induced oral mucositis. The mucoadhesive propolis gel was able to control inflammation and oral infection. Few studies have shown efficacy of other green propolis formulations (extract and gel) for the treatment of patients with oral candidosis [28,29]. The results observed are related to the anti-inflammatory and antimicrobial properties of propolis [30-34]. The anti-inflammatory property seems to be related to large amounts of C-artepillin [35]. On the other hand, the antimicrobial properties seem to relate to the presence of flavonoids, flavones, flavanones. However, due to the complex chemical constitution shown propolis it becomes difficult to confirm the true roles of each compound, since they seem to act synergistically [24,26, 36,37].

Radiation therapy usually takes place during 5 to 7 weeks. In this study we chose to follow all patients for 9 weeks in order to better evaluate the eventual development of radiation-induced oral mucositis after the conclusion of radiation therapy. The occurrence of radiation-induced oral mucositis usually occurs between the 3rd and 6th weeks of treatment depending on the amount of irradiation [38-40]. During the period of study, it was not observed any alterations that could be attributable to the tested product. All patients reported that the feeling of "dry mouth" was not observed during the treatment. This probably happened because propolis possesses acidic content that could contribute to salivary flow. We not observed alterations or undesirable reactions in the hard and soft tissues of the mouth.

The influence of total dose and dose per fraction on radiation-induced oral mucositis development has been noted by various authors [38,39,41-43]. The total dose used in our protocol ranged from 5040 to 7020 Gy in daily fractions of 180cGy between 5 and 7 weeks. The severity of mucositis is dose-dependent. However, few patients developed mucositis while using the propolis gel.

Several authors have emphasized the importance of proper maintenance of good oral hygiene in alleviating the oral problems due to radiation [41,44-46]. Patients in our study were submitted to scaling and root planing, treatment of carious lesions, dental extractions and oral hygiene instructions before being referred for radiation therapy and initiating the use of mucoadhesive propolis gel. The oral hygiene status was monitored weekly during the whole period of radiation therapy.

The results observed in this study were very similar to those observed by our group in a previous study testing mouthwash containing 5% green propolis. Patients answered the same kind of questions [27]. Some patients complained of burning in the first days of use and then not be more complaints. The mucoadhesive gel containing 5% green propolis (MAGP) was accepted and tolerated by individuals. Although most subjects find the taste of unpleasant MAGP 5%, they were satisfied with the product, considering the occurrence of positive changes and oral health which performed better after the treatment period. There were complaints about the taste, color and mode of use of the gel, however, the positives outweighed the negatives. And that proved this by the number of patients who accepted the product. These findings coincide with those of Murray *et al.* [18], Cheng [26] and Enderli and Deniz [43,47].

CONCLUSION

This study suggests that mucoadhesive propolis gel could be a useful topical alternative for prevention of radiation-induced oral mucositis. A further phase III study should be carried out in order to evaluate this product in a larger number of patients and in comparison with other therapies currently available for this condition. The mucoadhesive gel containing 5% green propolis (MAGP) was accepted and tolerated by individuals.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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