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Allicin as a possible adjunctive therapeutic drug for stage II oral submucous fibrosis: a preliminary clinical trial in a Chinese cohort

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Abstract. The objective of this study was to investigate the efficacy and safety of allicin in the treatment of stage II oral submucous fibrosis (OSF) in a Chinese patient cohort. A randomized clinical trial was performed. Triamcinolone acetonide (TA) or allicin was injected intralesionally weekly for 16 weeks. Improvements in mouth opening, burning sensation, and oral health-related quality of life were evaluated. Forty-eight subjects completed the study without obvious adverse reactions. At 40 weeks, the net gain in mouth opening was 2.27 ± 0.84 mm in the TA group and 5.16 ± 1.04 mm in the allicin group. Burning sensation improved by 2.79 ± 0.87 in the TA group and by 4.33 ± 1.04 in the allicin group. The OHIP-14 score improved by 4.67 ± 2.94 in the TA group and by 12.58 ± 9.82 in the allicin group. Allicin intralesional injections improved mouth opening, burning sensation, and oral health-related quality of life in these stage II OSF patients. Allicin appears to be a potential adjunctive therapeutic drug.

Key words: oral submucous fibrosis; allicin; triamcinolone acetonide; treatment.

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Oral submucous fibrosis (OSF), a chronic and insidious disease, is usually an intractable clinical problem. The histological characteristics of OSF include submucosal disorder and excessive collagen accumulation. The pathological fibrosis of the submucosa in the oral cavity, oropharynx, and frequently the upper third of the oesophagus inevitably results in limitations of mouth opening, tongue mobility, swallowing, and/or phonation and also an intolerance to spicy foods, an oral burning sensation, and xerostomia.[1]

The aetiology of OSF is multifactorial, and a betel quid chewing habit has usually been regarded as the main factor.[2] Betel quid (BQ) contains betel leaf, areca nut, slaked lime, and tobacco, and sometimes other ingredients and flavourings. OSF patients are found mostly in the developing nations of Asia,[3] where betel quid chewing is popular.

The treatment of OSF is usually empirical and varied. Enzymes, cardiovascular

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drugs, antioxidants, vitamins, microelements, etc., have been tested for the treatment of OSF.[4] To date, there is no widely recommended single treatment that is effective and significantly reduces morbidity. Garlic extract has recently been reported to reverse liver fibrosis in the hepatofibrosis model, with no obvious side effects.[5] In this preliminary clinical study, it was hypothesized that the main ingredient of garlic extract – allicin – may play a useful role in the treatment of OSF patients.

Table 1. Clinical stages of OSF according to Pindborg.

Stage	Clinical description
I	Stomatitis
II	Fibrosis (a) Early lesions, blanching of the oral mucosa (b) Older lesions, vertical and circular palpable fibrous bands in and around the mouth or lips, resulting in a mottled, marble-like appearance of the buccal mucosa
III	Sequelae of oral submucous fibrosis (a) Leukoplakia (b) Speech and hearing deficits

OSF, oral submucous fibrosis.

Materials and methods

A randomized clinical trial was conducted; the trial was approved by the Institutional Ethics Committee/Institutional Review Board of the First People's Hospital of Chenzhou, University of South China. The study was designed as a double-blind trial and the results were analyzed by per-protocol analysis. The clinical diagnosis of OSF was made by a history of betel nut chewing and clinical symptoms such as oral burning sensation, xerostomia, oral mucosa blanching or stiffness, and progressive inability to open the mouth. The clinical stage at diagnosis was determined according to the criteria of Pindborg (Table 1).

All patients were selected according to strict inclusion and exclusion criteria. The inclusion criteria were as follows: (1) age between 20 and 50 years and stage II OSF; (2) agreement not to use other curative agents during the procedure and ability to follow the investigator's instructions exactly and provide signed informed consent voluntarily; and (3) lesions mostly located in the cheek or pterygomandibular regions. Exclusion criteria were as follows: (1) allergy to garlic; (2) other accompanying mucosal disorders, such as oral leukoplakia, lichen planus, or erythroplakia, or a systemic disorder (diabetes mellitus, myasthenia gravis, AIDS, e.g.); (3) any treatment for OSF before the current study; (4) the use of systemic non-steroidal anti-inflammatory drugs or immunomodulatory agents during the past 2 weeks; and (5) pregnancy or lactation.

A total of 52 participants (six women and 46 men) were enrolled from patients with OSF attending the department of stomatology of the study hospital in Chenzhou during 2011–2014. All of the patients were enrolled from the tobacco cessation clinic before the commencement of treatment. The patients in this clinical trial were numbered sequentially from 1 to 52 according to the time of enrolment. Twenty-six numbers smaller than 52 were then selected from a random number table generated by computer. These 26 patients whose number was the same with the number selected from the random number table were assigned to one study group and the remaining 26 patients were assigned to the other. This process was done by an operator who was blinded to the treatment protocol and who was not involved in the evaluation of the effect of treatment. The required laboratory tests, such as complete blood cell count, serum chemistry levels, and urinalysis, were performed before and after treatment.

All patients received an intralesional injection 5 min after the application of local anaesthetic cream (20% Topcaine; Medental, Balama City, USA); this was repeated at weekly intervals for a total of 16 weeks. Patients in group A received an intralesional injection of triamcinolone acetonide (2 mg; Tianjin Kingyork Group Co. Ltd). Patients in group B received an intralesional injection of allicin (1 mg TCM-046, 99% HPLC; Nanjing TCM Institute of Chinese Materia Medica). The chemical formula of allicin (chemical name thio-2-propene-1-sulphinic acid S-allyl ester) is $C_6H_{10}S_2O$. The different agents were dissolved in 3 ml saline and injected bilaterally. The chosen injection point was the buccal lesional region near the angle of the mouth. The lesion area was divided into three approximately equal portions. After the needle had been inserted into the submucosa, the solution was injected in the three directions while maintaining the same needle entry point (approximately 0.5 ml solution was injected in each direction).

All subjects were instructed to perform daily mouth exercises[6] (mouth stretching for each patient was done three times a day for 15 min) and to abstain from harmful oral habits (betel nut chewing, cigarette smoking, and alcohol consumption) under the supervision of doctors and family members. The details of age, gender, oral habits, and level of education were recorded. At the end of the trial, laboratory tests and clinical examinations were performed and patient complaints recorded in order to evaluate injection safety. The patient was also informed that they could terminate the trial immediately if any adverse reaction occurred.

Maximum mouth opening (MO) was measured by one operator who was blinded to the group assignment, using a sliding caliper with millimetre markings.[7] The linear distance between the incisal edges of the upper and lower central incisors was measured three times, and the average value recorded. A burning sensation was usually evident in patients suffering from OSF. In the clinical trial, the alleviation of this burning sensation was evaluated by the patient using a self-administered visual analogue scale (VAS) questionnaire.[7] The VAS consisted of a 10-cm horizontal line between the poles of 'normal sensation' and 'worst burning sensation'. Baseline parameters were obtained and recorded on the day of the first visit (week 0). Oral health-related quality of life was assessed utilizing the Oral Health Impact Profile (OHIP)-14 questionnaire.[8] Evaluations of MO and the VAS were done at weeks 8, 16, and 40 after initiating treatment; the OHIP evaluation was performed at weeks 0 and 40.

All data were recorded as the mean $\pm$ standard deviation (SD). The effectiveness indices (EI) of maximum mouth opening and amelioration of burning sensation at each time point were calculated using the formulae: EI (MO) = $W_x - W_0$ and EI (burning sensation or OHIP) = $W_0 - W_x$ (where W_0 was the value at the first visit and W_x the value at 8, 16, or 40 weeks). Comparisons of background and demographic data between the two groups were performed with the Mann–Whitney test using SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA). One-way analysis of variance was performed to assess differences in EI values in the groups. A P-value of less than 0.05 was considered statistically significant.

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