

EVALUATION OF THERAPEUTIC EFFECT OF SPIRULINA IN PATIENTS WITH GEOGRAPHIC TONGUE: A RANDOMIZED DOUBLE BLIND CONTROLLED CLINICAL TRIAL

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ABSTRACT

Objective: The aim of this study is to evaluate the therapeutic effect of spirulina in patients with Geographic Tongue

Materials and Methods: Twenty patients diagnosed with symptomatic benign migratory glossitis will be selected. Research ethical committee will review the protocol and the procedure will be explained to the patients and they will sign an informed consent. Seven days after the diagnosis and selection of patients with (BMG), the atrophic areas will be determined and the patients will attend a control checkup in order to exclude those with constant changing patterns of the red atrophic areas with raised keratotic margins. The selected patient according the inclusion and exclusion criteria will be randomly allocated using computer generated allocation concealment into two groups; Group I (study group): Will include 10 patients with symptomatic BMG receiving Spirulina tablet Supplementation triple daily. Group II: Will include 10 patients with symptomatic BMG receiving placebo treatment for one month. (control group). Intensity of the discomfort will be monitored by the patients using the Visual Analogue Scale (VAS). Saliva will be collected from all included patients to evaluate interleukin -8 (IL -8).

KEYWORDS: Spirulina, geographic tongue, Benign migratory glossitis, burning mouth syndrome, tongueinflammation.

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INTRODUCTION

Geographic tongue, better known as benign migratory glossitis (BMG), remains an idiopathic inflammatory condition that often affects the tongue's epithelium and is mostly asymptomatic. Lesions with atrophic glossitis and a rapid change in colour and size are characteristic and occur due to the local loss of filiform papillae. The histopathologic results may have a psoriasiform pattern and correspond with the clinical presentation. The condition is characterized by flare-ups and remissions. Other than being reassured that the illness is benign, most patients don't need therapy (*Picciani et al. 2021*).

Geographic tongue is a pathological condition also known as temporary benign plaque of the tongue, benign wandering glossitis, erythema migrans, annulus migrans, and exfoliation areata linguae (*Purani and Purani 2014*). While BMG most commonly affects dorsum of the tongue, also, it may manifest on the sides of the tongue. Circular reddish patches with slightly elevated white margins that resemble a map are a common clinical manifestation (*Abe et al. 2007; Jaikittivong and Langlais 2005; Sigal and Mock 1992*).

Diagnosis usually involves a clinical examination, complete history of numerous migratory lesions which vary in size, affected region, and clinical appearance. Most cases are not symptomatic and are discovered during routine clinical evaluation, necessitating only confirmation that the lesion is benign and self-resolving (*Picciani et al. 2021*).

Studies have linked BMG to psoriasis, hormonal imbalance, dietary deficiencies, allergens, Reiter's syndrome, anaemia, seborrheic dermatitis, pregnancy, Down syndrome, stress, and diabetes. Numerous studies have indicated BMG prevalence between 1 to 4.8% (*Jaikittivong and Langlais 2005; Miloğlu et al. 2009; Picciani et al. 2021; Redman 1970*). BMG is more prevalent in women than in men (2:1). Young people and those under 30 seem to have it more often (*Miloğlu et al. 2009*).

Although the lesion is asymptomatic, some people with geographic tongues report discomfort ranging from sensitivity to highly acidic foods, such as citrus, to tobacco smoke (*Shulman and Carpenter 2006*). If symptoms increase, acetaminophen, diphenhydramine hydrochloride, lidocaine gel mouth rinses, topical corticosteroids such as betamethasone, cyclosporine, tretinoin, zinc, and vitamin K supplements may be prescribed. There is a lack of consensus in the literature regarding the treatment of symptomatic geographic tongue (*Nandini et al. 2016*).

Spirulina is a type of filamentous cyanobacteria that has been widely utilized as a dietary supplement. Specifically, *Spirulina platensis* and *Spirulina maxima* hold the utmost significance. Spirulina is utilized as a nutraceutical dietary supplement due to its rich protein and vitamin content. Additionally, its various possible health advantages have garnered significant interest. Its antioxidant as well as anti-inflammatory properties have been revealed to treat diabetes, hypertension, and arthritis (*Hatami et al. 2021; Moradi et al. 2019; Wu et al. 2016a*).

Spirulina phycocyanin stops the production of proinflammatory cytokines, lowers COX-2 levels, and stops the production of prostaglandin E2. It also eliminates free radicals such as hydroxyl, alkoxy, and peroxy radicals, demonstrating antioxidation properties. B-carotene, another spirulina component, suppresses the synthesis of nitric oxide and prostaglandin E2. As a result, anti-inflammatory action is produced (*Hamedifard et al. 2019*).

Interleukin-8 (IL-8) is a well-known proinflammatory cytokine produced by phagocytes and mesenchymal cells exposed to inflammatory stimuli that activates neutrophil chemotaxis, exocytosis, and the respiratory burst (*Matsushima, Yang, and Oppenheim 2022*). IL-8 probably plays a crucial role in geographic tongue, as evidenced by increased levels of IL-8 in unstimulated saliva collected from patients with the disease (*Dafar et al. 2017*).

To the best of our knowledge, a limited number of randomized clinical trials have evaluated the therapeutic effects of spirulina supplements in patients with BMG. So, we designed this study to determine spirulina supplements' effect on the management of the burning sensation associated with BMG and to assess the salivary levels of IL-8 in these patients after receiving the supplement.

Aim of the Study

This study was performed to determine whether spirulina supplementation is beneficial in treating patients with symptomatic benign migratory glossitis.

- The primary outcome measured was the clinical changes in the size of atrophic areas and subjective changes in the symptoms' intensity as evaluated by the Visual Analogue Scale (VAS).
- As a secondary goal, assessment of salivary IL-8 levels prior to and following therapy with spirulina supplementation was accomplished.

SUBJECTS AND METHODS

Sample size calculation and study design:

Study design: A randomized controlled clinical and biochemical study.

Sample size calculation:

Comparing the two patient groups, Spirulina supplementation efficacy on symptomatic migrating glossitis using an independent t-test with a significance level (error) of 0.05 for the data and a sample size of 20 (10 per group) will detect an effect size between 0.75 and 0.81 with 0.8 power (1-error). The sample size was obtained using G Power 3.1.2.9. (*Faul F.,2007*).

Patient selection:

Twenty patients with symptomatic benign migrating glossitis were selected from the Oral

Medicine, Periodontology, and Oral Diagnosis Department clinics, Faculty of Dentistry, Menoufia University, Misr University for Science and Technology, and Tanta University. The protocol was accepted by the research ethics committee at Tanta University and was conducted according to the declaration of Helsinki and all patients understood the nature of the study and signed the informed consent.

Inclusion Criteria

1. Both genders qualify.
2. Adults over 18 years of age.
3. Patients with persistent tongue atrophies and elevated keratotic margins.
4. Patients with symptomatic geographic tongues.

Exclusion Criteria

These patients were excluded:

1. Anemia, oral candidiasis, or local bothers (defective dental fillings, dental caries, sharp tooth edges, dental calculus, and poor prosthetic treatments).
2. Patient vulnerability (prisoners, disabled people, children, neonates, pregnant women)

Patient grouping:

In this multicenter, double-blinded, placebo-controlled, randomized trial, eligible patients were randomly assigned (1:1) by a computer-based randomization method, into 2 groups:

1. **Group 1 (Study group):** included ten patients with symptomatic BMG who were given Spirulina supplementation tablets (500 mg twice daily) for one month (*Shetty et al. 2013*).
2. **Group 2 (Control group):** included ten patients with symptomatic BMG taking placebo tablets for one month.

Treatment protocol:

Baseline data were gathered, including age, gender, illness status, medical history, medication history, family history, as well as clinical symptoms and indicators. Before initiation of treatment, eligible patients received the following:

Clinical assessment:**Objective assessment:**

Changes in the red atrophic areas' length and width were measured by a calibrated UNC-15 periodontal probe. Each subject's two largest atrophic zones were measured. Additionally, the largest irregular atrophic zone diameters were also recorded. (Cankovic et al, 2018)

Subjective pain assessment:

Patients recorded pain from 0 to 10 on the Visual Analogue Scale (VAS) in 1 cm increments, with "0" signifying no discomfort and "10" unendurable, the highest agony. Patients chose VAS values based on symptom severity. (Cankovic et al, 2018)

After one month of therapy and one month off, baseline objective and subjective tests were performed.

Biochemical assessment of salivary samples:

All patients' saliva were tested for IL-8 at baseline and one month after treatment.

Salivary sample preparation: Saliva samples were obtained from 8:00 to 11:00 a.m. using unstimulated spitting (discharge of saliva per minute for 5 minutes). The subjects were fasting and relaxed for at least 2 hours prior to sampling. The laboratory received graded, sterile plastic vials with the samples sealed. The saliva samples were centrifuged for 15 minutes at 4500 rpm to remove insoluble debris and phlegm and create a clear solution. Samples were stored at -20°C until investigation. Enzyme-Linked Immunosorbent Assay (ELISA) kits for the detection of IL-8 were used according to the

manufacturer's protocol. After development of the colorimetric reaction, the absorbance at 405nm was quantitated by spectrophotometer (ELISA reader) and the readings were converted to picograms per milliliter based on standard curves obtained with recombinant each assay.

Statistical Data Analysis:

The statistical analysis of the provided data was managed utilizing IBM SPSS software package version 24.0 (Armonk, NY: IBM Corp.) and GraphPad Prism 18. Descriptive statistics, including means, standard deviations, and counts, were generated for the groups. Group associations were carried out using the one-way analysis of variance (one-way ANOVA), followed by Tukey's post hoc test for multiple comparisons. In addition, the data was analyzed using paired t-tests to compare the mean differences within each group. Independent t-tests were used to compare the mean differences between the two groups.

RESULTS

Table 1 presents the baseline characteristics of patients randomized into two groups in a clinical trial. Statistical analysis reveals several key findings: The mean age of patients in Group 1 (32.9 ± 11.46 years) is higher than that in Group 2 (27.3 ± 11.29 years). There are more females than males overall. Both groups have a female predominance, with Group 1 having a 9:1 ratio and Group 2 having a 7:3. Patients report a wide range of chief complaints, with Group 1 having a higher mean duration (10.1 ± 7.06 years) than Group 2 (5.9 ± 3.35 years). There is diversity in medical history. The most frequent conditions are similar between groups, except for osteoarthritis only in Group 2 and neuritis only in Group 1.

In terms of atrophied areas, the most common locations are right side (9 patients), left side (7 patients), and tip (3 patients). Only Group 1 has atrophy of the dorsal surface (1 patient).

TABLE (1) Baseline characteristics of randomized patients in the study:

| | | Group 1 | Group 2 | |
|---------------------------|---------------------------------|------------|------------|---|
| Age (M±SD) | | 32.9±11.46 | 27.3±11.29 | |
| Gender | Male (N) | 1 | 3 | |
| | Female (N) | 9 | 7 | |
| Chief Complain Hx. (M±SD) | | 10.1±7.06 | 5.9±3.35 | |
| Free | | 2 | 5 | |
| Covid 19 | | 2 | 3 | |
| Osteoarthritis | | | 2 | |
| Sinusitis | | | 1 | |
| Nasal Allergy | | | 1 | |
| Neuritis | | 1 | | |
| Medical Hx. (N) | Hypertension | 1 | | |
| | Diabetes Mellitus | 1 | | |
| | GERD | 2 | | |
| | Long Bones Surgery | 1 | | |
| | Thyroidectomy | 1 | | |
| | Pancreatitis | 1 | | |
| | Depression | 1 | | |
| | Location of Atrophied Areas (N) | Right Side | 4 | 5 |
| | | Left side | 3 | 4 |
| | Tip | | 2 | 1 |
| Dorsal Surface | | 1 | | |

M; Mean, SD; Standard Deviation, N; Count

Table (2) presents the means and standard deviations of three key outcome variables (geographic tongue diameter, visual analogue scale, and salivary IL-8 levels) measured at baseline, 1 month, and 2 months in the two randomized groups. It also shows p-values testing for significant differences between groups at each timepoint.

The data were analyzed using independent t-tests to compare between the two groups at each timepoint, and one-way ANOVA with Tukey’s post-hoc test to compare within each group across the three time points.

For geographic tongue diameter, there was no significant difference between the two groups at baseline, with $p=0.5226$. However, after one month

and two months, group 1 showed a statistically significant decrease compared to group 2, with $p=0.0021$ and $p=0.0002$ respectively. Within group 1, geographic tongue diameter decreased significantly from baseline to one month and two months ($p=0.05$). But there was no significant change within group 2.

Similarly, for visual analogue scale, there was no difference between groups at baseline, but after one month and two months, group 2 showed a statistically significant greater decrease than group 1, with $p=0.0001$ for both. Within each group, visual analogue scale decreased significantly from baseline to one month and two months ($p=0.0097$ for group 1, $p=0.0026$ for group 2).

For salivary IL-8 levels, there was no significant difference between groups at baseline or after one month. Within group 1, there was a significant decrease from baseline to one month ($p=0.0019$). But no significant change was seen within group 2.

Table (3) displays the mean differences (MD) within each group from baseline to 1 month and baseline to 2 months on the three variables. The standard error of the difference (SED) is also shown.

For geographic tongue diameter, there was a significant decrease from baseline to one month in group 1 (mean difference: -58.36 , $p=0.0249$) but not in group 2. The difference between groups was also significant ($p=0.0249$). From baseline to two months, the decrease was still significant within group 1 but not between groups.

For visual analogue scale, there were no significant differences within or between groups in the change from baseline to one month or two months.

For salivary IL-8 levels, there was a significant decrease within group 1 from baseline to one month (mean difference: 11.93 , $p=0.0001$) but not within group 2. The difference between groups was also significant ($p=0.0001$).

TABLE (2) Means and standard deviation of measured variables at baseline, after one month and after two months in the test and control groups:

| Variables | Follow up | Group 1 | Group 2 | P-value |
|----------------------------|------------------|----------------|----------------|-------------|
| Geographic Tongue Diameter | Baseline | 133.36±96.16 A | 112±38.5 A | 0.5226 (NS) |
| | After One Month | 7S±28.94 B | 128.S4±37.32 A | 0.0021* |
| | After Two Months | 73.91±17.21 B | 122.7±28.16 A | 0.0002* |
| | P-value | 0.05* | 0.5692 (NS) | |
| Visual Analogue Scale | Baseline | 6.2±2.3S A | S±1.699 A | 0.2071 (NS) |
| | After One Month | 4.S±O.OSI A | 4.2±O.0686 A | 0.0001* |
| | After Two Months | 4.4±O.17 A | 3.2±O.619 B | 0.0001* |
| | P-value | 0.0097* | 0.0026* | |
| Salivary IL-8 Levels | Baseline | 442.72±8.27 | 437.08±30.67 | 0.5814 (NS) |
| | After One Month | 430.79±6.31 | 442.61±10.34 | 0.0064* |
| | P-value | 0.0019* | 0.6257 (NS) | |

M; Mean, SD; Standard Deviation, P; Probability Level

Means with same letters in the same column were insignificant different using Tukey's post hoc test for multiple comparisons.

Means with different letters in the same column were significant different using Tukey's post hoc test for multiple comparisons.

NS; Insignificant Different using independent t-test and One Way ANOVA

**; Significant Different Independent t-test and One Way ANOVA*

TABLE (3) Mean Differences of measured variables at baseline, after one month and after two months in the test and control groups:

| Variables | Follow up | Group 1 | | Group 2 | | P-value |
|----------------------------|---------------------------|-------------|--------|-------------|--------|-------------|
| | | MD | SED | MD | SED | |
| Geographic Tongue Diameter | Baseline-After One Month | -58.36 | 26.31 | 16.54 | 15.64 | 0.0249* |
| | Baseline-After Two Months | -59.45 | 26.31 | -10.7 | 15.64 | 0.1286* |
| | P-value | 0.9770 (NS) | | 0.2340 (NS) | | |
| Visual Analogue Scale | Baseline-After One Month | 1.7 | 0.6085 | 0.8 | 0.4672 | 0.2560 (NS) |
| | Baseline-After Two Months | 1.8 | 0.6085 | 1.8 | 0.4672 | 1.0000 (NS) |
| | P-value | 0.9088 (NS) | | 0.1475 (NS) | | |
| Salivary IL-8 Levels | Baseline-After One Month | 11.93 | 3.29 | -5.53 | 1.24 | 0.0001* |

MD; Mean Difference, SED, Standard Error of Difference, P; Probability Level

NS; Insignificant Different using independent t-test

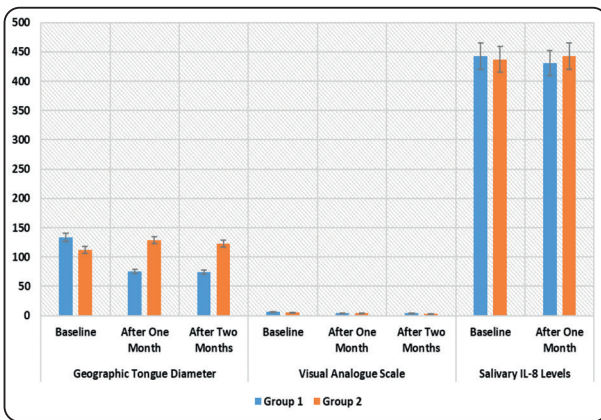


Fig. (1): Bar chart illustrating means and standard deviation of measured variables at baseline, after one month and after two months in the test and control groups.

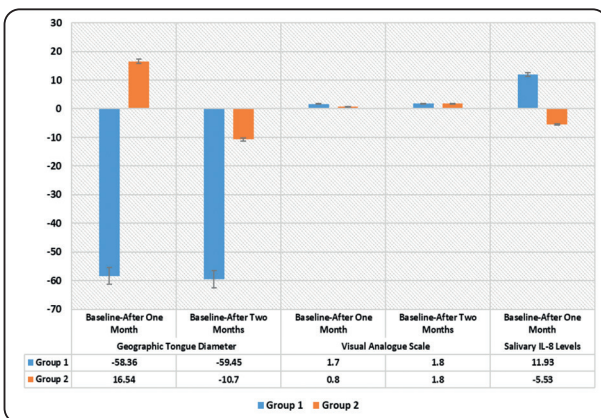


Fig. (2): Bar chart illustrating mean difference measured variables at baseline, after one month and after two months in the test and control groups.

DISCUSSION

Geographic tongue remains a poorly understood clinical pathological condition, for which little is known regarding the appropriate treatments for its symptomatic types. Several recent epidemiological studies have identified a significant association between Spirulina use and the overall incidence of antioxidant, anti-inflammatory, and anti-apoptotic effects. (Behairy et al. 2023) Given the commonness of the disease, its unpredictable nature, and its inherent risk for unpleasant pain sensation in some

patients, 20 patients with BMG were evaluated in our study both clinically and biochemically in the Spirulina and placebo study groups over a period of 2 months.

The selected cohorts of patients with BMG in our study contain more females of a younger age (median age, 32.9 years) who are seeking specialist help for their symptoms and concerns about their tongue lesions. This sex and age ratio correlates well with most of the studies on the disease. (Picciani et al. 2016).

Spirulina tablets are cheap, available, and well tolerated by patients. A follow-up period of one month was adopted because the maximum efficacy of Spirulina seems to appear after a month of its systemic administration (Grosshagauer, Kraemer, and Somoza 2020) (Mohiti et al. 2021). Another month of observation was carried out without administration of Spirulina to monitor its washout effect. Using placebo in the control group is supported by the slow and unpredictable course of the disease, putting in mind the spontaneous remission of several lesions.

The primary outcome of the current study was the clinical response based on the comparison of the lesion size at baseline and at after one and two months. The results revealed a significant association between the atrophic lesions size and the use of systemic Spirulina tablets. In the Spirulina group, geographic tongue diameter decreased significantly from baseline to one month and two months ($p = 0.05$). From baseline to two months, the decrease was still significant within group 1 but not between groups. This appreciates the possible anti-inflammatory and oral mucosal regenerative effects of Spirulina (Nasirian et al. 2018, Deng and Chow 2010). Our results are consistent with many other studies by Campbell et al. 2020, Patil et al. 2015, Moher et al. 200, Deng and Chow 2010) who found that spirulina reduced ulcers, erosions, and vesicles more than lycopene.

Another clinical parameter measured in the current study is the visual analogue scale. On the other hand, for visual analogue scale, there was no difference between groups at baseline, but after one month and two months, the placebo group showed a statistically significant greater decrease than the spirulina group. The greater decrease in the placebo group in VAS -though not showing the greatest reduction in lesion size- could be attributed to the fact that VAS can't be accurately reproduced, and results found weak correlation between VAS and change in pain. (*Gallagher et al. 2002*)

The clinical measures, although useful in detecting evidence of the present disease, provide only limited information about the tissue-level inflammatory status. Hence, in the present study, both clinical parameters and molecular markers were taken to capture evidence for the anti-inflammatory potential of Spirulina within a reasonable period of time and an affordable number of patients. On the molecular level, we evaluated the salivary levels of interleukin-8 in the placebo and Spirulina arm groups at baseline and 1 month. In fact, saliva is one of the most frequently recommended screening media for oral lesions and offers relevant information due to its direct oral lesions contact. Saliva has a number of benefits, including easy access, noninvasiveness, patient comfort, safe handling with low risk of transmitting disease, convenience for multiple sampling, and minimum training. We should, however, be aware of the disadvantages, such as the lack of standard methods, variability in the levels of salivary markers, and validation under inflammatory conditions.

Within the group of patients receiving Spirulina, there was a significant decrease in salivary levels of IL-8 from baseline to one month ($p = 0.0019$) with no statistically significant change seen within group 2. The authors agree with (*Abdel-Daim et al. 2015, Wu et al. 2016b*) that Spirulina downregulates the expression of IL-8.

Given the promising results of Spirulina use within the limits of the present clinical trial, together with its safety profile, route of administration and long history of safe use, the drug could be considered an ideal candidate for treatment of symptomatic geographic tongue via its inhibitory effect on the proinflammatory cytokine IL-8 both in oral mucosal tissues and saliva.

If these approaches of systemic Spirulina usages in dentistry succeed, they will be put into everyday clinical practice and will undoubtedly help reduce many inflammatory and probably neoplastic oral diseases in the not so distant future

CONCLUSIONS

Spirulina showed efficacy in managing the lesion size of geographic tongue in addition to the downregulation of salivary IL-8 levels. Spirulina could be implemented successfully as an anti-inflammatory drug in geographic tongue as well as other inflammatory conditions.

CONFLICT OF INTEREST

The authors claim no commercial or financial conflicts of interest in the research.

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