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Original Article

Efficacy of Multivitamin Supplementation in the Management of Recurrent Aphthous Stomatitis: A Randomized Controlled Trial

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Abstract

Background: Recurrent aphthous stomatitis (RAS) is a prevalent oral mucosal condition marked by painful ulcerations that adversely affect patients' quality of life. Despite its frequency, effective and consistent management of RAS remains a clinical challenge.

Objective: To assess the efficacy of multivitamin supplementation in reducing the frequency, duration, and severity of aphthous ulcers in patients diagnosed with RAS.

Methodology: A randomized controlled trial was conducted at Bacha Khan College of Dentistry, Mardan, over a ten-month period. A total of 60 patients aged 18–60 years with clinically diagnosed RAS and no history of systemic illness, immunomodulatory therapy, pregnancy, or lactation were enrolled. Participants were randomly assigned to either the multivitamin group or the control group. Primary outcomes included ulcer resolution rate, symptom improvement, and time to symptom resolution. Continuous variables were analyzed using the Student's t-test, while categorical variables were expressed as percentages and analyzed using the chi-square test.

Results: The mean age of participants was 35.2 ± 5.8 years in the multivitamin group and 36.7 ± 6.1 years in the control group ($p = 0.42$), with male participants comprising 60% and 66.7%, respectively ($p = 0.61$). After six months, ulcer resolution was achieved in 73.3% of the multivitamin group compared to 33.3% in the control group ($p = 0.002$). Symptom improvement was reported by 83.3% in the multivitamin group versus 50% in the control group ($p = 0.01$). The average time to symptom resolution was significantly shorter in the multivitamin group (7.2 ± 2.3 days) than in the control group (10.5 ± 3.1 days; $p = 0.001$).

Conclusion: Multivitamin supplementation appears to be an effective adjunctive therapy in the management of RAS, significantly improving ulcer resolution, reducing symptom duration, and enhancing overall patient outcomes.

Keywords: Aphthous, Dietary Supplements, Multivitamins, Stomatitis, Treatment Outcome.

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Introduction

Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal disorders, affecting up to 25% of the general population, with a recurrence rate as high as 50% within three months [1]. The condition presents as painful ulcerations in various parts of the oral cavity, including the tongue, inner cheeks, lips, and occasionally the throat [2]. RAS is classified into three main types: minor, major, and herpetiform. Minor aphthous ulcers are the most common form, typically measuring less than 10 mm in diameter, shallow in appearance, and healing within 7–14 days without scarring. In contrast, major ulcers exceed 10 mm, take longer to heal, and often result in scarring. Herpetiform ulcers consist of multiple pinpoint-sized lesions that may coalesce into larger ulcers [3]. Clinically, RAS appears as well-circumscribed, painful ulcers with an erythematous border and a yellow or grayish base, significantly impairing quality of life by interfering with eating, speaking, and maintaining oral hygiene [4].

The diagnosis of RAS is primarily clinical, as no specific laboratory test exists to confirm it. Diagnosis involves taking a detailed history to rule out underlying medical conditions or recent medication use and performing a physical examination to exclude systemic causes such as Behçet's disease, celiac disease, and inflammatory bowel disease [5]. Additional laboratory investigations, such as complete blood count and serum levels of iron, folate, and vitamin B12, may be conducted to rule out nutritional deficiencies [6].

There is currently no definitive cure for RAS. Management focuses on relieving symptoms and reducing recurrence. Standard treatments include topical corticosteroids, antiseptic mouthwashes, and local anesthetics. Severe or refractory cases may require systemic therapies such as immunomodulators or Colchicine. Adjunctive interventions like laser therapy and cryotherapy have also been employed in persistent cases [7].

In recent years, multivitamin supplementation—particularly with vitamin B12, folate, and iron—has gained attention for its potential role in managing RAS. Nutritional deficiencies have been implicated in up to 20% of RAS cases, suggesting that supplementation may address underlying contributing factors [8]. Vitamin B12, in particular, is thought to reduce the frequency, duration, and severity of ulcers. Its proposed mechanisms of action include promoting DNA synthesis, enhancing tissue repair, and modulating immune responses [9]. Multivitamins may serve as an effective adjunctive therapy by supporting mucosal healing and symptom relief [10].

Given the high recurrence of RAS and the absence of a permanent cure, there is a need for safe, cost-effective, and easily accessible treatment options. Multivitamins, especially vitamin B12, have shown promise in improving long-term outcomes in RAS patients. Investigating their efficacy not only explores a potential therapeutic strategy but also aligns with broader goals of addressing nutritional deficiencies as modifiable risk factors. Currently, there is a lack of local literature on this subject. This study aims to provide baseline data that may inform clinical decision-making in local healthcare settings.

The objective of this study was to evaluate the efficacy of multivitamin supplementation in reducing the frequency, duration, and severity of aphthous ulcers in patients with RAS.

Methodology

Trial Design

This study was a single-center, parallel-group, randomized controlled trial conducted over a period of ten months, from January 15, 2024, to November 30, 2024, at Bacha Khan College of Dentistry, Mardan. The trial aimed to assess the efficacy of multivitamin supplementation in patients with recurrent aphthous stomatitis (RAS). Participants were recruited through a non-probability consecutive sampling technique.

Participants

A total of 60 participants, aged 18–60 years, clinically diagnosed with idiopathic RAS, were

enrolled. Diagnosis was based on characteristic clinical features: shallow, painful, well-demarcated ulcers with erythematous margins located in the oral mucosa. Exclusion criteria included patients with a history of systemic conditions such as Behçet's disease, inflammatory bowel disease, autoimmune disorders, or those currently receiving systemic immunomodulatory therapy (e.g., corticosteroids, Colchicine, or TNF-α inhibitors). Pregnant and lactating women were also excluded. Informed written consent was obtained from all participants after explaining the study's purpose, procedures, potential risks, and benefits.

Interventions

Participants were randomized into two groups. The intervention group (Group A) received a daily oral dose of multivitamins (Bevidox®, one tablet per day) in addition to standard topical corticosteroid therapy. The control group (Group B) received only topical corticosteroids. Both groups were monitored for ulcer resolution, symptom improvement, and recurrence over the course of the study. Participants were followed up monthly to assess treatment response, adherence, and side effects. All patients received counseling on maintaining oral hygiene and avoiding trauma to the oral mucosa.

Outcomes

The primary outcomes were ulcer resolution (complete healing of ulcers), improvement in symptoms (pain relief and reduction in ulcer size), and time to symptom resolution. Secondary outcomes included the frequency of ulcer recurrence during follow-up and the number of ulcers per episode. These outcomes were evaluated through clinical examination and patient self-report at each monthly follow-up visit.

Sample Size

Sample size estimation was conducted using OpenEpi software. Based on findings from a previous study [11], which reported ulcer resolution in 74.1% of the intervention group compared to 32% in the control group, a minimum sample size of 44 participants (22 per group) was calculated at 80% power and a 95% confidence interval. However, to ensure normality assumptions and account for potential dropouts, a total of 60 participants (30 per group) were recruited.

Randomization

Participants were randomly assigned to either the experimental or control group using block randomization to ensure equal allocation throughout the recruitment phase. Blocks of four (e.g., AABB, ABBA, BBAA) were used, with "A" indicating the multivitamin plus topical steroid group and "B" indicating the topical steroid-only group. A random sequence of block combinations was generated prior to enrollment and concealed in sealed envelopes to maintain allocation concealment.

Blinding

This was an open-label trial. Due to the nature of the intervention, blinding of participants and investigators was not feasible. However, outcome assessment was standardized using predefined clinical criteria to reduce observer bias.

Ethics

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Bacha Khan College of Dentistry, Mardan. Ethical principles outlined in the Declaration of Helsinki were strictly followed. All participants gave informed consent prior to inclusion in the study.

Statistical Methods

Data analysis was performed using SPSS version 21.0 (IBM Corp., Chicago, IL, USA). Continuous variables (e.g., age, time to ulcer resolution) were expressed as mean ± standard deviation (SD), while categorical variables (e.g., gender, symptom improvement) were presented as frequencies and percentages. Group comparisons for continuous variables were performed using the Student's t-test, and categorical variables were analyzed using the chi-square test. A p-value of <0.05 was considered statistically significant.

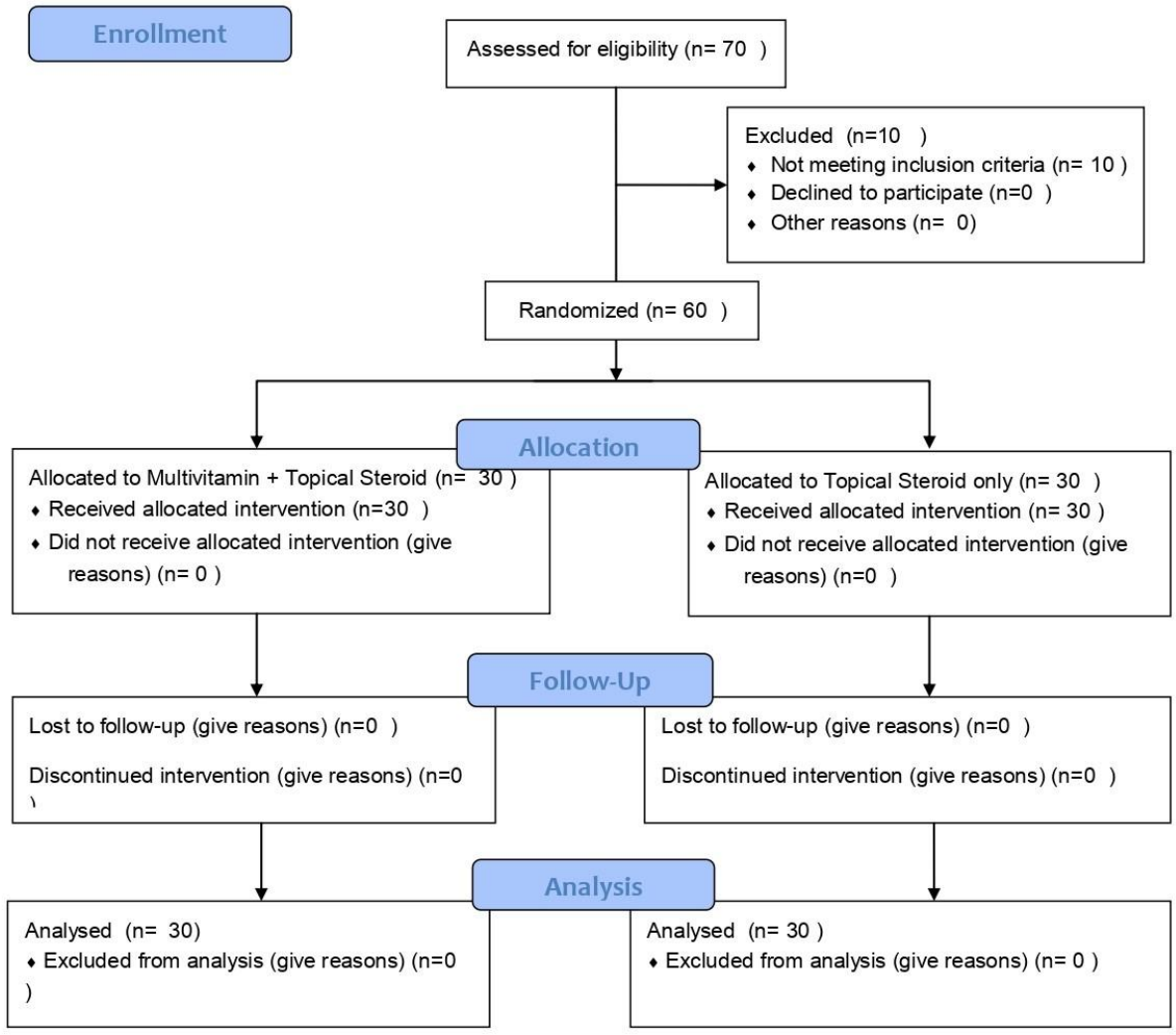


Figure 1: CONSORT flow for patients selection.

Results

Recruitment

A total of 60 participants with clinically diagnosed recurrent aphthous stomatitis (RAS) were enrolled in the study over the ten-month recruitment period, from January 15 to November 30, 2024, at Bacha Khan College of Dentistry, Mardan. All eligible participants who met the inclusion criteria and provided informed consent were randomized into either the multivitamin group (n=30) or the control group (n=30). There were no losses to follow-up, and all participants completed the six-month follow-up period.

Baseline Data

The demographic and baseline clinical characteristics of both groups were comparable at the time of enrollment (Table 1). The mean age was 35.2 ± 5.8 years in the multivitamin group and 36.7 ± 6.1 years in the control group (p=0.42). Gender distribution was also statistically similar between groups, with males comprising 60% and 66.7% of the multivitamin and control groups, respectively (p=0.61). The average number of ulcers at baseline was 2.8 ± 1.2 in the multivitamin group and 3.1 ± 1.5 in the control group (p=0.34). These findings

confirm that both groups were well-matched before the intervention.

Numbers Analysed

All 60 randomized participants (30 in each group) were included in the final analysis. No participants were excluded after randomization, and no data were lost during follow-up, ensuring a 100% analysis rate according to the intention-to-treat principle.

Outcomes and Estimation

Significant differences were observed in treatment outcomes between the two groups over the six-month follow-up period (Table 2). By the end of the study, 73.3% (n=22) of participants in the multivitamin group achieved complete ulcer resolution, compared to only 33.3% (n=10) in the control group (p=0.002). Symptom improvement, as reported by the participants, was also significantly higher in the multivitamin group (83.3%) versus the control group (50%) (p=0.01). Furthermore, the mean time to symptom resolution was markedly shorter in the multivitamin group, averaging 7.2 ± 2.3 days, compared to 10.5 ± 3.1 days in the control group (p=0.001). These findings indicate that multivitamin supplementation significantly improved both clinical and subjective outcomes in RAS patients.

Ancillary Analyses

No pre-specified subgroup or ancillary analyses were performed in this study. However, exploratory stratification by gender showed no significant interaction with treatment outcomes, suggesting the observed benefits of multivitamin supplementation were consistent across male and female participants.

Harms

No adverse effects or harms related to the multivitamin intervention were reported during the study period. All participants tolerated the treatment well, and no participant discontinued therapy due to side effects. Regular follow-up and adherence checks ensured early identification of any potential safety concerns, none of which were observed.

Table 1: Demographics and baseline characteristics of participants in both groups

Variable		Multivitamin Group (n=30)	Control Group (n=30)	p-value
Age (years)		35.2 ± 5.8	36.7 ± 6.1	0.420
Gender	Male	18 (60)	20 (66.7)	0.610
	Female	12 (40)	10 (33.3)	
Number of ulcers		2.8 ±1.2	3.1 ±1.5	0.340

Student t test applied for analysis of continuous variables and Chi-square test applied for categorical variables.

Table 2: Comparison treatment outcomes in both groups during six months follow up

Outcome Variables		Multivitamin Group (n=30)	Control Group (n=30)	p-value
Ulcers at last follow-up	No	22 (73.3)	10 (33.3)	0.002*
	Yes	8(26.7)	20 (66.7)	
Symptom	Improved	25 (83.3)	15 (50)	0.010*
	Not improved	5(16.7)	15 (50)	
Time to symptom resolution (days)		7.2 ± 2.3	10.5 ± 3.1	0.001*

Student t test applied for analysis of continuous variables and Chi-square test applied for categorical variables.
*p<0.05 is considered statistically significant

Discussion

This randomized controlled trial evaluated the efficacy of multivitamin supplementation in the management of Recurrent Aphthous Stomatitis (RAS) and found significantly improved outcomes in the multivitamin group compared to the control group. Baseline demographic characteristics, including age and gender distribution, were comparable between the two groups, confirming homogeneity at study entry. However, after six months of follow-up, patients receiving multivitamin therapy demonstrated superior clinical outcomes.

Our principal finding was that multivitamin supplementation led to a significantly greater rate of ulcer resolution and symptom relief than standard topical therapy alone. A significantly higher proportion of participants in the multivitamin group achieved complete healing of ulcers ($p=0.002$), reported symptomatic improvement ($p=0.01$), and had a shorter time to symptom resolution by an average of 3.3 days ($p=0.001$). These results suggest that multivitamins may serve as an effective adjunct in the treatment of RAS by accelerating healing and reducing symptom burden.

Previous literature has shown mixed results regarding the efficacy of multivitamins in RAS management. For instance, Lalla et al. reported that daily multivitamin supplementation did not significantly affect the frequency or duration of RAS episodes [12]. However, it is important to note that their study utilized formulations providing only the recommended daily intake, which may not have been sufficient to correct underlying micronutrient deficiencies. Similarly, Spivakovsky et al. found no significant difference in ulcer count or duration between multivitamin and placebo groups in their randomized controlled trial [13]. These discrepancies may be attributed to differences in multivitamin composition, dosages, or population characteristics.

In contrast, Taleb et al. emphasized the critical role of vitamin B12 in RAS management, noting that higher doses (e.g., 1000 µg) could reduce ulcer frequency and duration [14]. Although our study did not isolate vitamin B12, it is plausible that the combination of high-dose B12 and other micronutrients in our multivitamin formulation contributed synergistically to the improved outcomes.

Moreover, Seo et al. demonstrated promising results using zinc-enriched multivitamins (ZnVita), with 58.7% of patients reporting partial or complete response [8]. Their findings align with ours, reinforcing the importance of specific micronutrients such as zinc in the pathophysiology and management of RAS. Zinc is known to possess anti-inflammatory and immune-modulating properties, which may help reduce ulcer recurrence and improve mucosal healing.

While our findings are encouraging, several limitations must be acknowledged. First, the multivitamin supplement used in this study contained a combination of vitamins and minerals, making it difficult to identify which specific components were most responsible for the observed therapeutic benefits. Future research should consider isolating key nutrients—such as vitamin B12, folate, and zinc—to determine their individual or synergistic effects on RAS. Additionally, dose–response studies are needed to optimize treatment regimens and explore alternate delivery routes (e.g., sublingual or injectable formulations).

This study has several strengths, including a randomized controlled design, clear eligibility criteria, monthly follow-ups, and a larger sample size than initially calculated. The use of block randomization ensured equal allocation, and outcome assessment was standardized. Ethical approval was secured, and informed consent was obtained from all participants, adhering to principles of ethical research conduct.

Limitations

However, the study is limited by its single-center design and the use of non-probability consecutive sampling, which may reduce the generalizability of findings. Moreover, the lack of trial registration

could impact transparency. Another limitation is the absence of laboratory testing to confirm nutritional deficiencies or inflammatory markers, which could have provided objective measures of treatment response or stratification.

Conclusion

This study demonstrates that multivitamin supplementation significantly enhances treatment outcomes in patients with recurrent aphthous stomatitis. Individuals receiving multivitamins experienced faster symptom resolution, greater symptomatic relief, and higher rates of complete ulcer healing compared to those receiving standard care alone. These findings suggest that multivitamins represent a safe, accessible, and effective adjunctive therapy for managing RAS, particularly in patients with potential underlying nutritional deficiencies.

Authors' Contributions

All authors meet the ICMJE criteria for authorship. They have reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Author 1: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 2: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 3: Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 4: Analysis and interpretation of data, critical revision, final approval, agreed to be accountable for all the work.
Author 5: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 6: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.

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