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# Probiotics as an adjuvant treatment for recurrent aphthous ulcer: A randomized clinical trial

**Abhishek Singh\***

Reader, Department of conservative dentistry and Endodontics Sardar Patel Institute of Dental and Medical Sciences, Lucknow.

\*Corresponding Author

**Amit Agarwal**

HOD, Dept of Oral maxillofacial Surgery, Seema Dental College and Hospital Rishikesh.

**Eedala Abhishek**

Senior lecturer, Department of Orthodontics and Dentofacial Orthopedics, Gitam Dental College and Hospital.

**Shubhangi Jain**

Senior Lecturer, Department of Orthodontics and dentofacial orthopedics. I.T.S dental College, Ghaziabad.

**Rohie Jawarker**

Consultant, Happy Smiles Clinic, Dept of Oral Maxillofacial Surgery.

**Monis Raza**

Senior Lecturer. Department of Orthodontics and Dentofacial Orthopedics. ITS Dental College, Ghaziabad.

**Abstract**--*Background:* The most common ulcer in adults, recurrent aphthous ulcers affect roughly 25% of them. The purpose of this study was to see how beneficial probiotics are at treating it. *Materials and Procedures:* 160 people in total were split into two groups. Bacillus coagulans (Sporolac) and Tetracycline capsules 250 mg (Tetrastar) were given twice daily to 80 patients in Group 1 for 7 days. In Group 2, 80 patients received just Tetracycline capsules 250 mg (Tetrastar) twice a day for 7 days. At the beginning, fourth, and seventh days of the ulcer, discomfort, size, and average duration were recorded. In order to compare the parameters between the two groups, the Mann-Whitney U test was performed. *Results:* Over the course of just four days, all of the metrics for the Probiotic group dropped substantially.

*Conclusion:* RAS can be treated and managed with probiotics as adjuvant therapy.

**Keywords**---aphthous ulcers, biofilm, probiotics, tetracyclines, ulcers.

## **Introduction**

Recurrent aphthous stomatitis (RAS), sometimes called as canker sores, is the most common mucosal lesion in the mouth. Ulcers are shallow, painful, and surrounded by a halo of inflammation with a serous discharge on the ulcer floor. The disease is classified into three kinds depending on its clinical manifestations: mild, major, and herpetiform. Minor recurrent aphthous ulcers (MiRAU) are the most common type of recurrent aphthous ulcers (RAU), affecting 75–80% of people. <sup>1</sup> MiRAU commonly affects patients between the ages of 5 and 19. A few superficial, circular ulcerations measuring less than 10mm with a grey pseudo membrane and erythematous halo characteristic outbreak.<sup>2</sup> Buccal mucosa, Lips, and, tongue are the most common sites for minor aphthae.<sup>3</sup>

Although various reasons have been postulated, including immunologic abnormalities, environmental and psychological stress, and viral infections, the disease's genesis is obscure and controversial. <sup>1</sup> When fed in suitable amounts, probiotics are living bacteria that help the host's health. Probiotics interact with and strengthen the immune system, which aids in the prevention of illness. <sup>4</sup> Probiotics create organic acids, bacteriocins, and peptides, among other things. As a result, there is less likelihood of dangerous bacteria colonization. <sup>5</sup> Tetracyclines reduce pain by limiting oxidative activation, lowering prostaglandin synthesis, suppressing leukocyte activity, inhibiting collagenase and gelatinase activities, and inhibiting collagenase and gelatinase activity. The purpose of this study was to explore if probiotics may be utilized as a treatment for RAS.

## **Materials and Method**

The investigation was conducted in private dental clinics and dental hospitals and was designed as a randomized control trial. RAS was identified based on the clinical signs and symptoms as well as the medical histories of the patients. Participants in the RAS study must have one or more aphthous ulcers that have been present for less than 48 hours and have a diameter of 1 cm or bigger. One hundred sixty people were enrolled and randomly assigned to two groups using the parallel randomization approach. The researchers used controls that were of the same age and sex as the participants. Before starting treatment, all patients were given written and verbal information about the study and were asked to sign an informed consent form.

### *Inclusion criteria:*

- a) Minimum age between the ages of 18 and 65 years
- b) Patients who are not on any other drugs or treatment.

### *Exclusion Criteria:*

- a) Patients that are younger or older than the age range

- b) Patients with systemic disorders or syndromes
- c) Oral mucosal ulcers other than RAS
- d) Women who are pregnant or nursing

Bacillus was given to the 80 patients in Group 1. (48 men and 32 females). For seven days, Sporlac twice daily with tetracycline 250 mg (Tetrastar) was given. Sporlac was administered one hour after antibiotic therapy. Before ingesting, the probiotics were mixed in 10 mL of water and swished for 1–3 minutes in the oral cavity. A tetracycline capsule's contents were also ingested in the same manner. In Group 2 (46 males and 34 females), only tetracyclines capsules 250 mg (Tetrastar) was administered twice a day for 7 days. Before ingesting, the capsule's contents were mixed in 10 mL of water and swished for 1–3 minutes in the mouth.

The Visual Analog Scale (VAS) was used to grade the quantity, location, size with divider and range, and discomfort on a scale of 0 to 10, with 0 being nonexistent, 1 being light, 5 being moderate, and 10 being severe. To indicate how difficult it was to eat, yes/no was utilized. The most recent ulcer was chosen in patients who had more than one ulcer. Patients were invited to return on the fourth and seventh days to assess ulcer healing, discomfort, and feeding issues. A drop in all metrics in both groups was used to establish the treatment's success. Regular phone calls were arranged to keep track of how the drug was being administered.

### **Statistical Analysis**

The data were investigated using IBM SPSS statistics (Statistical Package for Social Science) version 22.0. (Armonk, NY: IBM Corp). Descriptive data was supplied as frequency and percentage for categorical variables, and mean, median, standard deviation, and quartiles were utilized for continuous variables. To compare categorical variables between the research groups, the Chi-square test, and the fishers' test was utilized. To compare the parameters between the two groups at each time interval, the Mann-Whitney U test was performed. A P value of less than 0.05 was considered statistically significant.

### **Results**

The research began with 160 participants ranging in age from 18 to 65 years old. The average age of onset of aphthous ulcers in this study was  $32.67 \pm 9.68$  years. Eleven patients from Group 1 and 9 patients from Group 2 had to be removed from the experiment due to noncompliance with the research protocol. The final research population consisted of 69 individuals from Group 1 and 71 patients from Group 2. Baseline values were gathered for each patient on the first day of reporting, including a history of eating problems, the number of ulcers, the size of the ulcers in both groups, and the pain severity as VAS ratings. Patients in the study and control groups were recalled on the 4th and 7th days to record their history of eating problems, the number of ulcers, the size of the ulcers, and the pain severity as VAS ratings. These were statistically analyzed and compared to the baseline levels.

There was no significant difference in ulcer size decrease between the first and fourth days in both groups (Table 1). The results were significant on the seventh day, revealing that group 1 had a total reduction in ulcer size when compared to group 2. Group 1 had 49 (71.01%) and group 2 had 47 (66.2%) ulcers with a diameter of less than 1cm at the initial visit, respectively. The proportion of patients having ulcers larger than 1cm in groups 1 and 2 was 20 (28.99%) and 24 (33.8%) individuals, respectively. The ulcer size on the fourth day was zero in 40 (57.97%) and 23 (32.39%) of groups 1 and 2, and 1cm in 29 (42.03%) and 48 (67.61%) of group 2 ( $p = 0.18$ ). On the seventh day, the ulcer size was zero in 12 patients in group 1, 100 percent (69 patients), 59 patients in group 2 (83.1%), and 1cm in 12 patients in group 2. (16.9 percent). There was a statistically significant reduction in ulcer size on the seventh day ( $p = 0.04$ ). From day 1 to day 7, the number of ulcers in group 1 decreased significantly as compared to group 2. (See Table 1)

In both groups, minor pain was reported in 21 (15%) patients, moderate pain in 43 (30.71%) patients, and severe pain in 76 (54.29%) patients at the initial visit. On the second visit, 86 (61.43 percent) patients had no pain, 34 (24.29 percent) had light pain, and 20 (14.28 percent) had significant pain. At the third appointment, the pain score was zero in 140 patients (100.0%). There was a statistically significant difference in pain reduction ( $p = 0.01$ ) during the second visit (Table 2).

Table 1: Ulcer Size Comparison Between Groups 1 and 2 at Different Time Intervals

Visit	size	Group		Total	Chi-Square Test	
		1	2		Chi Square value	P value
First visit	1	49 (71.01 %)	47 (66.2%)	96 (68.57%)	-	0.07
	2	20 (28.99 %)	24 (33.8%)	44 (31.43%)		
Second visit	0	40 (57.97 %)	23 (32.39%)	63 (45%)	2.66	0.18
	1	29 (42.03 %)	48 (67.61%)	77 (55%)		
Third visit	0	69 (100 %)	59 (83.1%)	128 (91.43%)	-	0.05*
	1	0 (0 %)	12 (16.90%)	12 (8.57%)		

#(size: 1 =<1cm, 2=>1cm, 0=0). \* $p < 0.05$  statistically significant

Table 2: The Mann-Whitney U test was used to compare the size, number, and pain of ulcers in Group 1 and Group 2 at different time intervals.

	Group	n	Mean±SD	U statistic	P
Size in 1 <sup>st</sup> visit	1	69	1.24 ±0.34	104.7	0.47
	2	71	1.36±0.48		

Size in 2 <sup>nd</sup> visit	1	69	0.36±0.45	86	0.8
	2	71	0.66±0.53		
Size in 3 <sup>rd</sup> visit	1	69	0.0±0.0	77.02	0.05*
	2	71	0.39±0.40		
No. of ulcers in 1 <sup>st</sup> visit	1	69	1.15±0.31	105.6	0.56
	2	71	1.18±0.47		
No. of ulcers in 2 <sup>nd</sup> visit	1	69	0.56±0.49	107.5	0.66
	2	71	0.48±0.42		
No. of ulcers in 3 <sup>rd</sup> visit	1	69	0.0±0.0	88.8	0.04*
	2	71	0.25±0.46		
VAS in 1 <sup>st</sup> visit	1	69	2.50±0.77	118.5	0.1
	2	71	2.52±0.65		
VAS in 1 <sup>st</sup> visit	1	69	0.24±0.56	56.8	0.01*
	2	71	0.98±0.74		
VAS in 1 <sup>st</sup> visit	1	69	0.0±0.0	116	0.9
	2	71	0.0±0.0		

## Discussion

Because RAS is so common, there has been a lot of research into viable therapies. RAS is a painful inflammatory disorder characterized by necrotizing ulcers of the oral mucosa that can appear at any time and can last for weeks, months, or years. <sup>6</sup> The most prevalent type of RAS is nonkeratinized mucosa. RAS patients with major aphthae account for 10% to 15% of all RAS cases, with ulcerations that are larger, last longer, and sometimes leave a scar. Five to ten percent of all aphthous ulcer cases are herpetiform aphthae, which are marked by multiple 1–3 mm painful ulcers that resemble the outbreaks of herpes simplex but include nonkeratinized mucosa and can last up to 14 days. <sup>7</sup>

Probiotics are ranked as the second most critical component of the immune system by the World Health Organization (WHO) as a result of antibiotic resistance.<sup>8</sup> Probiotics can produce a biofilm that serves as a barrier between the oral mucosa and oral infections. <sup>9</sup> Combining probiotics with antibiotics can reduce the effects of antibiotic-induced dysbiosis while also maximizing the benefits of gut immune activation. <sup>10</sup> Probiotics reduce inflammation by influencing epithelial cells and mucosal immune system dysfunction, two factors that contribute to inflammation. <sup>11</sup>

Probiotics boost nonspecific immunity and regulate humoral and cellular immunological responses, making them beneficial to the immune system. <sup>12</sup> In our study, both groups showed significant decreases in ulcer size, although Group 1 showed a significant reduction in ulcer size on the seventh day compared to Group 2 ( $p = 0.05$ ). The amalgamation of probiotics and tetracyclines was proven to be therapeutically helpful in accelerating ulcer healing.

Both groups had a considerable improvement in discomfort within 3 - 4 days. There was a statistically significant difference in pain reduction between the two groups at the second visit ( $p = 0.01$ ). Both groups experienced a decrease in the number of ulcers and difficulties eating by the seventh day. Reduced synthesis of

nitric oxide (NO), a potent inflammatory mediator that regulates the production of inflammatory cytokines such as PGE<sub>2</sub>, IFN, MMPs, and TNF, has been associated with pain alleviation. Our findings on day 5 of treatment are similar to those of Nirmala M et al., who discovered that when *Bacillus Clausii* was given to the patients, the mean number of ulcers and ulcer size decreased equally in both groups, whereas erythema and degree of pain decreased significantly in group A patients compared to group B patients ( $p = 0.001$  and  $0.0001$ , respectively).<sup>9</sup> Furthermore, our findings are consistent with those of Nalini et al., who discovered that giving patients probiotic lozenges reduced the size of ulcers. On day 10<sup>th</sup> of the trial, both groups of patients improved their symptoms, with no significant differences between them.<sup>13</sup>

## Conclusion

Oral aphthosis can be caused by a variety of conditions, with a wide range of underlying disorders. Clinicians have a various therapy choice to choose from. A therapy ladder that ranges from topical to systemic drugs may help clinicians decide which treatment is best for their patients. Using probiotics as an adjuvant in the treatment of aphthous ulcers, the study demonstrated their efficacy and speed of response. Probiotics and tetracyclines were found to lower the number, size, and discomfort associated with ulcers while having no negative side effects, according to the study. As a result, probiotics combined with tetracyclines may be an effective adjuvant treatment in RAS.

## References

1. Jiang X-W, Zhang Y, Song G-D, Li F-F, Peng H-Y, Yang S.-K, et al. Clinical evaluation of allicin oral adhesive tablets in the treatment of recurrent aphthous ulceration. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;113:500-4.
2. Yasui K, Kurata T, Yashiro M, et al. The effect of ascorbate on minor recurrent aphthous stomatitis. *Acta Paediatrica*. 2010;99(3):442-445.
3. Wallace A, Rogers HJ, Hughes SC, et al. Management of recurrent aphthous stomatitis in children. *Oral Medicine*. 2015;42(6):564-572.
4. Prathap S. Probiotics and oral health. *J Orofac Res* 2011;1:20-5.
5. Sasikala G, Sivaraman M, Dutta T, Dhanasekar KR. Comparative prospective randomized open label trial of synbiotic (bifilac) as an add on therapy with standard treatment in patients with aphthous ulcer. *Int J Basic Clin Pharmacol* 2017;7 (5):878-81.
6. Natah SS, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Hayrinen-Immonen R. Recurrent aphthous ulcers today: A review of the growing knowledge. *Int J Oral Maxillofac Surg* 2004;33:221-34.
7. Gorsky M, Epstein J, Raviv A, Yaniv R, Truelove E. Topical minocycline for managing symptoms of recurrent aphthous stomatitis. *Spec Care Dentist* 2008;28:27-31.
8. Saraf K, Shashikanth MC, Priy T, Sultana N, Chaitanya NC. Probiotics-Do they have a role in medicine and dentistry? *J Assoc Physicians India* 2010;58:488-90, 495-6.

9. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2022). Post-pandemic health and its sustainability: Educational situation. *International Journal of Health Sciences*, 6(1), i-v. <https://doi.org/10.53730/ijhs.v6n1.5949>
10. Nirmala M, Smitha SG, Kamath GJ. A study to assess the efficacy of local application of oral probiotic in treating recurrent aphthous ulcer and oral candidiasis. *Indian J Otolaryngol Head Neck Surg* 2017;71:113-7.
11. Green A. Probiotics and Antibiotics-Should they be Given Together? *Protexin Health Care*. 2010:33-5.
12. Batara, R., Ardani, I. G. A. I., Wardani, I. A. K., Windiani, I. G. A. T., Adnyana, I. G. A. N. S., & Setiawati, Y. (2022). Psychogenic dysphagia in children, and the success of family-based treatment: Case report. *International Journal of Health & Medical Sciences*, 5(1), 163-168. <https://doi.org/10.21744/ijhms.v5n1.1894>
13. Boirivant M, Strober W. The mechanism of action of probiotics. *Curr Opin Gastroenterol* 2007;23:679-92.
14. Bonifait L, Chandad F, Grenier D. Probiotics for oral health: Myth or reality? *J Can Dent Assoc* 2009;75:585-90.
15. Nalini A, Praveen Kumar ST, Jayesh S, Manigandan T, Sarumathi T. A randomized, open label, clinical study of synbiotics in patients with recurrent minor aphthous ulcers. *Res J Pharm Biolog Chem Sci* 2014;5:1901-5.