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Clinical Study

Use of Lozenges Containing *Lactobacillus brevis* CD2 in Recurrent Aphthous Stomatitis: A Double-Blind Placebo-Controlled Trial

Vito Trinchieri,[1] Stefano Di Carlo,[2] Maurizio Bossu',[2] and Antonella Polimeni[2]

[1] *Department of Public Health and Infectious Diseases, Sapienza, University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy*
[2] *Department of Oral and Maxillofacial Sciences, Sapienza, University of Rome, Viale Regina Elena, 287/A, 00161 Rome, Italy*

Correspondence should be addressed to Vito Trinchieri, vito.trinchieri@uniroma1.it

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Recurrent aphthous stomatitis is a common disorder of the oral cavity, affecting mainly young people. It is characterized by small ulcers which can be very painful and generally heal spontaneously within 7–14 days. There is currently no therapy that can provide rapid healing. This study evaluated the efficacy and rapidity of response of a lozenge containing *Lactobacillus brevis* CD2. 30 patients were randomized to take 4 lozenges a day of active product or placebo for 7 days. Signs and symptoms as well as laboratory parameters in the saliva were assessed at the start of the study and after 7 days of treatment. The study demonstrated the efficacy and the rapidity of response of the *Lactobacillus brevis* CD2 lozenges in resolving the clinical signs and symptoms of aphthous stomatitis, with a significantly rapid improvement of pain. This is the first study confirming the efficacy of a probiotic product in this pathology.

1. Introduction

Recurrent aphthous stomatitis (RAS) is characterized by spontaneously self-limiting ulcerations of the mucosa of the oral cavity. The lesions can be single or multiple and generally affect the nonkeratinized mucosa of the cheeks, the soft palate, the fauces, the mouth floor, the tongue, and the gums.

This pathology can be observed in 20–30% of the population and most commonly affects the higher social classes [1, 2]. The highest incidence is among young people between 10 and 20 years of age, the severity and frequency of ulcers decreasing with age [3–6]. Genetic predisposition is also involved; if both parents suffer from recurrent aphthous stomatitis, the probability of an early onset of such pathology is as high as 90%, but this probability falls to 10% if only one parent suffers from it [7].

Recurrent aphthous stomatitis can be divided into three categories according to the characteristics of the ulcer: major, minor, and herpetiform. The major form is characterized by painful ulcers (>10 mm) which erode the mucosa creating deep ulcers located on the palate, tonsils, pharynx, or tongue, which generally heal—often forming a scar—within 2 weeks, but can sometimes take months. The minor form is the most common and represents about 80% of all cases of recurrent aphthous stomatitis. Clinically, it presents painful, small (5–10 mm), well-defined ulcers, which are round or oval in shape; they usually affect the buccal or labial mucosa and heal in about 7–10 days. The herpetiform type is named after its likeness to *Herpes Simplex Virus* (HSV) ulcerations. Recurrences can generally be observed every 1–4 months, but some patients present with virtually continuous ulceration [8–11].

A detailed clinical history should be taken for each case of recurrent aphthous stomatitis in order to exclude other diseases that can present aphthous-like lesions such as Behçet's syndrome, Crohn's disease, human immunodeficiency virus (HIV) infection, and neutropenia [6, 12, 13].

The etiology of recurrent aphthous stomatitis is still unknown, although many predisposing factors have been

described: trauma, stress, changes in the immune system, sensitivity to certain types of food, or ingested substances such as preservative agents or cinnamaldehyde (a substance contained in some toothpastes), iron, zinc, and vitamin deficiency [14–16]. The main pathogenetic event is the inflammatory response with production of inflammatory cytokines (IL2- IL12, IFN-γ), prostaglandin E2 (PGE2), and nitric oxide (NO) [17–19].

The treatment of recurrent aphthous stomatitis remains unsatisfactory and frustrating for both patients and doctors. Patients are asked to brush delicately and avoid eating any hard, sharp, or irritating foods. Topical steroids at best reduce the pain but not the rate of recurrence; moreover they can cause systemic effects. Topical tetracycline and chlorhexidine may reduce the severity of the inflammation but not the frequency. In severe cases, systemic steroids, thalidomide, colchicine, pentoxifylline, azathioprine, alpha 2 interferon, and cyclosporine are considered as possible options for the patients, but again the side effects can be significant.

Previous studies have shown *Lactobacillus brevis* CD2, administered as lozenges, to treat aphthous ulcerations on the mouth of patients affected by Behçet's disease was effective in reducing the number and frequency of the ulcers [20].

The *Lactobacillus brevis* CD2 strain used for these studies has specific known characteristics and is endowed with high levels of arginine deiminase, an enzyme that plays a fundamental role in the metabolism of arginine. Indeed, many of the bacteria involved in the pathogenesis and in the maintenance of the inflammatory processes of the oral cavity (such as periodontitis, Behçet's syndrome, recurrent aphthous stomatitis, and radio/chemotherapy-induced mucositis) require arginine for their own survival and intrinsic pathogenicity. The high content of arginine deiminase explains the many specific actions performed by this strain, in particular (i) a reduction of the availability of arginine within the oral cavity, thus preventing the growth of arginine-dependent inflammatory microorganisms; (ii) reduced availability of arginine to arginase, with consequent minor production of polyamines; (iii) reduced availability of arginine for NO-synthase, thus reducing the production of nitric oxide (NO) and leading to a direct attenuation of the inflammatory processes which have damaging and destructive consequences in cases of acute and chronic mucositis (Figure 4).

The primary aim of this study was to evaluate the efficacy and time to remission with a lozenge containing at least 1 billion *Lactobacillus brevis* CD2 in patients with a clinical condition related to aphthous stomatitis.

Secondary endpoints included assessment of the variations of prostaglandin E2 (PEG2), Interferon-γ (IFN-γ), and nitrite/nitrate levels in the saliva.

2. Materials and Methods

The study was conducted in a double-blind, placebo-controlled fashion on 30 patients, 15 (7 male and 8 female) aged between 8 and 36, treated with lozenges containing *Lactobacillus brevis* CD2 and 15 (8 male and 7 female) aged between 10 and 35 treated with lozenges containing placebo. The patients were visited and enrolled in a private practice in Rome, Italy.

2.1. Treatment Plan. 1 lozenge containing *Lactobacillus brevis* CD2 (Inersan—VSL Pharmaceuticals, Inc.) or placebo was administered 4 times daily for a total period of 7 days, including in the case of reduced symptoms. Patients were instructed to melt the lozenge in the mouth slowly and away from food intake.

Each lozenge was composed of the following: lyophilized bacteria of *Lactobacillus brevis* CD2, at least 1 billion live bacteria per lozenge. Excipients: mannitol, aspartame, fructose, talc, silicon dioxide, magnesium stearate, and banana flavour.

Placebo consisted of a lozenge containing excipients only, supplied in the same packaging and administered in the same way and at the same dosage as the active product.

2.2. Inclusion and Exclusion Criteria. The criteria for inclusion in the study included a history of recurrent minor aphthous stomatitis (at least 3 episodes in a year), characterized by painful ulcers of 1–10 mm in diameter that had arisen no more than 48 hours prior to enrolment and which generally had an expected clinical resolution of 5 or more days.

Exclusion criteria for this study were patients with diabetes mellitus, alcohol and/or drug abuse, or patients who had undergone dental interventions or taken antibiotic therapy in the two weeks prior to enrolment. Also excluded from the study were patients who had taken anti-inflammatory steroid and nonsteroid therapy within 30 days prior to enrolment.

All patients were informed about the study and the characteristics of the product and signed informed consent at enrolment.

All patients were subjected to evaluation of clinical and laboratory parameters at the start of therapy (T0), and at the end of treatment (T1).

2.3. Clinical Parameters. The following clinical signs and symptoms were taken into account: spontaneous pain, local burning, and perilesional erythema. The intensity of the signs and symptoms was expressed as 0: absent, 1: mild, 2: moderate, 3: severe.

Moreover the total sum of the diameters of the greater individual ulcers, expressed in millimeters, was calculated at enrolment and at the end of treatment.

Particular attention was given to the assessment of pain: patients were asked to score the intensity of spontaneous pain based on the Numerical Rating System scale from 1 to 10, considering a rating from 1 to 4 as mild pain (score = 1), >4 to 7 as moderate (score = 2) and >7 to 10 as severe pain (score = 3).

A questionnaire about observed daily changes in pain was handed out, in which patients were asked to fill in, sign and return at the end of treatment.

2.4. Laboratory Parameters. Salivary samples were collected in all patients to assess PGE2, IFNγ, and nitrite/nitrate levels.

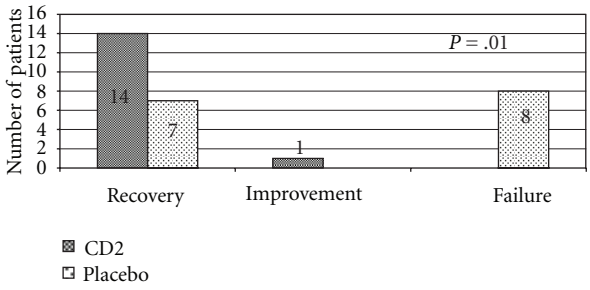

Figure 1: Clinical evaluation.

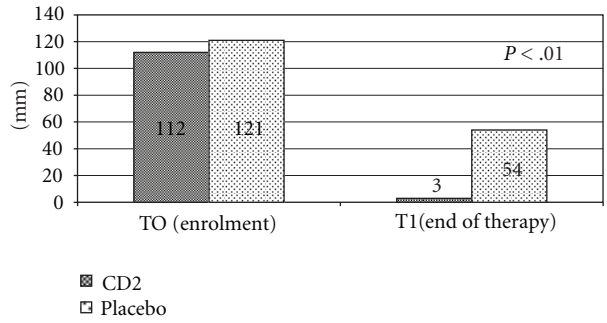

Figure 2: Sum of greater diameters.

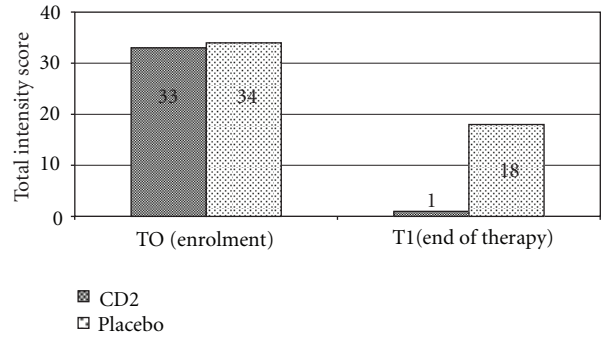

Figure 3: Intensity of spontaneous pain.

2.4.1. Determination of INFγ and PGE2 Levels in the Saliva. IFNγ (Endogen Inc., Woburn, Man, USA) and PGE2 (Assay Designs) were determined in the fluid saliva fraction using ELISA kits, in accordance with the manufacturer's instructions.

2.4.2. Determination of Nitrite/Nitrate Levels in the Saliva. In aqueous solutions, NO reacts rapidly with O2 and accumulates in the culture medium as nitrite and nitrate ions. Twenty microliters of saliva samples or supernatants from macrophage cultures were used for nitrite measurement by colorimetric assay based on the Griess reaction. Briefly, 5 ml of HEPES (50 mM, ph 7.4), 5 μL of FAD (5 μM), 10 μL NADPH (0,1 mM), 58 μL of H_2O, and 2 μL of nitrate reductase (0,2 IU ml^{-1}) were added to 20 μL of samples, which were then incubated for 30 minutes at 37°C. At the end of the incubation time 10 μL of pyruvic acid (100 mM) and 1 μL of LDH (1500 IU ml^{-1}) were added to the samples. After 10 minutes of incubation at 37°C, samples were mixed with an equal volume of Griess reagent in a microtiter place and incubated at room temperature in the dark for 10 minutes. The OD was measured at 550 nm using a microenzyme-linked immunosorbent assay (ELISA) reader (Easy Reader EAR 400; Kontron Analytic, London, UK): KNO_3 dissolved in H_2O was used as standard and H_2O as Blank.

2.5. Statistical Analysis. Differences in the analyzed parameters between active and control groups were tested using the Student's *t*-test. The statistical significance of the differences in clinical and laboratory parameters between T0 and T1 was analyzed using the paired sample *t*-test. The statistical program was used to perform statistical analysis and statistical difference was set at $P < .05$.

3. Results

All patients enrolled in the study completed the trial.

From a clinical point of view, 14 of 15 patients (93.3%) treated with *Lactobacillus brevis* CD2 showed complete remission of the clinical symptoms and 1 patient showed a remarkable improvement. In the placebo group, 7 (46.6%) showed complete healing, while in the remaining 8 patients symptoms persisted at the end of treatment. The difference between the two groups was statistically significant ($P = .01$) (Figure 1).

The sum of diameters of the greater individual ulcers at enrolment was 112 mm in the *Lactobacillus brevis* CD2 group and 121 mm in the placebo group; the two groups were not statistically different at this stage (P = NA). At the end of therapy, the sum of diameters of the greater individual ulcers in the *Lactobacillus brevis* CD2 group was 3 mm, while in the group of patients treated with placebo, it was 54 mm ($P < .01$) (Figure 2).

The pattern and the intensity of individual clinical signs and symptoms under review was as indicated in Table 1.

3.1. Patients Treated with Lactobacillus Brevis CD2

3.1.1. Local Burning. At enrolment burning was severe in 7 patients (intensity 21), moderate in 5 (intensity 10), and mild in 3 (intensity 3), with a total value of intensity equal to 34; at the end of therapy local burning persisted mildly only in 1 patient (intensity 1) with total value of intensity equal to 1.

3.1.2. Spontaneous Pain. At enrolment spontaneous pain was severe in 6 patients (intensity 18), moderate in 6 (intensity 12), and mild in 3 (intensity 3) with a total value of intensity equal to 33; after treatment it persisted as mild only in 1 patient (intensity 1) with a total value of intensity equal to 1 (Figure 3).

3.1.3. Perilesional Erythema. At enrolment this was severe in 6 patients (intensity 18), moderate in 7 (intensity 14), and mild in 2 (intensity 2), with a total value of intensity equal to 34; at the end of therapy perilesional erythema persisted

Table 1: Summary of clinical parameters before and after administration of *Lactobacillus Brevis* CD2 or placebo lozenges.

		Lactobacillus brevis CD2 ($n = 15$)					Placebo ($n = 15$)					Intergroup comparison
		Severe (n)	Moderate (n)	Mild (n)	Absent (n)	Total Value	Severe (n)	Moderate (n)	Mild (n)	Absent (n)	Total value	
Burning	before	7	5	3	0	34	8	4	3	0	35	$P = .9$
	after	0	0	1	14	1	2	4	2	7	16	$P = .03$
Spontaneous pain	before	6	6	3	0	33	7	5	3	0	34	$P =$ na
	after	0	0	1	0	1	3	4	1	7	18	$P = .02$
Caused pain	before	9	6	0	0	39	10	5	0	0	40	$P =$ na
	after	0	0	1	14	1	5	2	1	7	20	$P = .02$
Perilesional erythema	before	6	7	2	0	34	7	5	3	0	34	$P =$ NA
	after	0	0	1	0	1	3	4	1	7	18	$P = .02$

Value assignment: 0: absent, 1: mild, 2: moderate, and 3: severe.

as mild only in 1 patient (intensity 1) with a total value of intensity equal to 1.

No side effects were observed and the tolerability of the therapy was judged as excellent by all patients.

3.2. Patients Treated with Placebo

3.2.1. Local Burning. At enrolment burning was severe in 8 patients (intensity 24), moderate in 4 (intensity 8), and mild in 3 (intensity 3), with a total value of intensity equal to 35; at the end of therapy local burning persisted as severe in 2 patients (intensity 6), moderate in 4 (intensity 8), and mild in 2 (intensity 2), with a total value of intensity equal to 16.

3.2.2. Spontaneous Pain. At enrolment pain was severe in 7 patients (intensity 21), moderate in 5 (intensity 10), and mild in 3 (intensity 3), with a total value of intensity equal to 34; after treatment spontaneous pain persisted as severe in 3 patients (intensity 9), moderate in 4 (intensity 8), and mild in 1 (intensity 1), with a total value of intensity equal to 18 (Figure 3).

3.2.3. Perilesional Erythema. at enrolment this was severe in 7 patients (intensity 21), moderate in 5 (intensity 10) and mild in 3 (intensity 3), with a total value of intensity equal to 34; after therapy it persisted as severe in 3 patients (intensity 9), moderate in 4 (intensity 8) and mild in 1 (intensity 1), with a total value of intensity equal to 18.

No side effects were observed and the tolerability of therapy was judged as excellent by all patients.

3.3. Development of Pain. The data provided by patients about the development of pain over time revealed a complete regression of pain in 14 of 15 patients treated with *Lactobacillus brevis* CD2 by the third day of treatment, while this occurred in only 5 of 15 patients treated with placebo ($P = .001$). Of the remaining ten patients treated with placebo, 2 had complete regression of symptoms within 5 days from the start of the treatment, while pain persisted at the end of therapy in 8 patients.

3.4. Laboratory Parameters. At the end of therapy, there was a marked reduction in levels of PGE2, IFNγ, and nitrite/nitrate in the saliva of patients treated with *Lactobacillus brevis* CD2, whereas this reduction was not significant in the group of patients who received placebo (Table 2).

4. Discussion

In the normal microflora of the mouth, it is possible to isolate several thousand microbial species. These microorganisms create a dynamic equilibrium with the host immune system, allowing for proper defence mechanisms against pathogens. Some of these bacteria have a rich array of enzymes which enables them, through metabolic activities, to modify their surrounding environment.

Some lactic acid bacteria, and in particular the *Lactobacillus brevis* CD2 species, are rich in arginine deiminase which catalyzes the irreversible conversion of arginine to citrulline and ammonia, therefore decreasing the availability of arginine and consequently ornithine, the starting material of the polyamine biosynthetic pathway. Moreover, arginine deiminase competes with nitric oxide synthase (NOS) for the common substrate, arginine, to downregulate the production of nitric oxide (NO), which represents a multifunctional messenger molecule, able to modulate the production of inflammatory cytokines, PGE2 and metalloproteinase, thus explaining the anti-inflammatory effects of *Lactobacillus Brevis* CD2 (Figure 4).

The main symptom of which patients complain is intense pain; this is inevitably associated with considerable difficulty, and sometimes outright inability, in swallowing both solid and liquid foods. Even speech may be impaired, especially during the period of greater intensity of the stomatitis, because the pain increases. It is evident that pain is the main component of the considerable discomfort these patients suffer from. Such discomfort may also create significant social problems for the patient from both professional and personal standpoints. For this reason, our study focused primarily on the rapidity of response and reduction of pain. The results obtained from the study show that there is a rapid disappearance of pain after just 2-3 days of treatment. Only

Table 2: E Summary of laboratory parameters before and after administration of *Lactobacillus Brevis* CD2 or placebo lozenges.

		L. brevis CD2	Placebo	Intergroup comparison
Nitrite/Nitrate (μM)	(T0)	42.38 ± 4,58	39.76 ± 5.08	$P = .14$
	(T1)	7.5 ± 1.5	27.5 ± 3.5	$P < .01$
PGE2 (ng ml^{-1})	(T0)	1.89 ± 0.2	1.77 ± 0.2	$P = .11$
	(T1)	0.40 ± 0.05	1.02 ± 0.3	$P < .01$
IFNγ (pg ml^{-1})	(T0)	32.25 ± 4.2	30.85 ± 4.2	$P = .36$
	(T1)	9.57 ± 1.7	21.07 ± 2.9	$P < .01$

T0: before treatment; T1: after treatment.

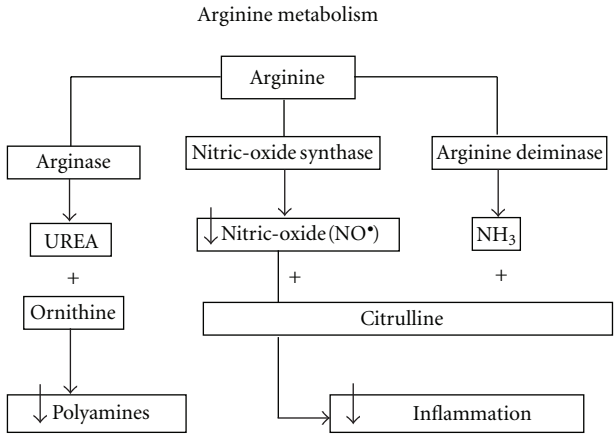

Figure 4

one patient who took the lozenge containing *Lactobacillus brevis* CD2 had continuing pain after 3 days of treatment against 10 patients in the placebo group.

The improvement in pain levels and especially the speed with which this improvement occurred is certainly the most interesting aspect that has emerged from this study and is related to the reduced production of Nitric Oxide (NO), one of the most powerful mediators of inflammation, which is able to modulate the production of inflammatory cytokines such as PGE2, IFNγ, MMPs, and TNFα.

Our findings clearly showed that all these inflammatory-associated markers were drastically reduced in recurrent aphthous stomatitis patients after treatment with *Lactobacillus brevis* CD2 lozenges when compared to patients treated with placebo.

The reduced production of Nitric Oxide (NO) depends on arginine deiminase, an enzyme in which *Lactobacillus brevis* (CD2), the active ingredient of the product, is rich.

There have been many attempts over the years to find an effective treatment for recurrent aphthous stomatitis.

Since the etiology of recurrent aphthous stomatitis remains unknown, its treatment consists of therapeutic measures that suppress the symptoms rather than bringing about a definitive cure. Choice of treatment depends on the severity of the disease, including the frequency of ulcer recurrence, the number of ulcers present, their location and duration, and the level of associated orofacial pain. Patients with mild-to-moderate symptoms and infrequent ulcers may only require palliative therapy for pain-like anesthetics, tissue, caustic, and cortisone adhesives. The use of immunosuppressive and anti-inflammatory drugs has demonstrated varying degrees of success in severe cases of recurrent aphthous stomatitis. Drugs commonly used include corticosteroids, dapsone, colchicine, thalidomide, pentoxifylline, low-dose interferon-α, and levamisole [8].

Because of their anti-inflammatory action, steroids are most often used in the treatment of recurrent aphthous stomatitis but their long-term administration can cause adverse reactions such as atrophy of the oral mucosa and minor resistance to infections. One must always take into consideration both the efficacy and the possible side effects of a medicine when choosing therapy, bearing in mind also that no therapy guarantees a total or long-term cure for recurrent aphthous stomatitis.

The results obtained in this study demonstrate the safety and clinical efficacy of a product which, thanks to its unique characteristics, would seem to address fully those requirements of effectiveness, rapidity, tolerability (complete absence of side effects), and convenience (oral administration) that could make it a valid therapeutic option in the treatment of recurrent aphthous stomatitis.

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