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ORIGINAL ARTICLE

Norwegian LongoVital® and recurrent aphthous ulceration: a randomized, double-blind, placebo-controlled study

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OBJECTIVE: LongoVital® (LV) is a herbal-based tablet enriched with the recommended daily doses of vitamins. The present study was undertaken to investigate possible prevention of recurrent aphthous ulceration (RAU) during 4 months daily intake of the Norwegian LV.
DESIGN: The study was a placebo-controlled, double-blind, randomized, clinical trial.
SUBJECTS: Sixty otherwise healthy patients with at least one attack of minor RAU per 2 months were included in the study.
METHODS: After an introduction period (IP) of 60 days, the patients were randomly divided into three groups and given either LV, the herbs of LV only, or placebo. Three test tablets were taken every day together with breakfast for 4 months [tablet period (TP)] and the patients followed up for another 4 months (F-UP). The number of new ulcers (NU) and ulcer-free days (UFD) were observed.
RESULTS: Fifty-two patients completed the study. Neither NU nor UFD showed any statistical significant differences between any of the groups in any of the periods. All three groups, however, showed a significant increase in UFD during the first 2 months of TP compared to IP. Within the LV group only, there was a further increase in UFD after 2 months intake of the tablets. The number of NU and UFD decreased significantly in both the LV and the herbal group in F-UP compared with TP.
CONCLUSION: Neither the Norwegian LV nor the herbal component alone was superior to placebo in the prevention of RAU. The results, however, indicate that neither the LV nor the herbal group benefited from the treatment.
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Keywords: aphthous ulcers; herbs; LongoVital; nutritional supplementation; vitamins

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Introduction

Recurrent aphthous ulceration (RAU) is the most common oral mucosal disease affecting about 20% of the general population with a prevalence of about 2% (Axell, 1976). The etiology of RAU remains unknown, and the spectrum of suggested symptomatic therapies is broad. However, the superiority of one to the other is dubious. LongoVital® (LV) (DK. Reg. No. 5178/75) is the first harmless systemic therapy which has shown to be of benefit in the prevention of RAU (Pedersen *et al*, 1990a). LV has been sold as a food supplement in the Scandinavian countries since 1975. The tablet is based on dried and ground herbs supplemented with the recommended doses of vitamins (Table 1). The herbal component of the tablets, however, varies slightly between the countries due to different regulations for food supplements. The previous study with LV on RAU was performed with the Danish LV which at that time contained arnica (Pedersen *et al*, 1990a). The only difference between the Danish and the Norwegian LV is that the Norwegian LV does not contain arnica. The present study was undertaken to investigate possible prevention of RAU during 4 months daily intake of the Norwegian LV or the herbal component alone and to elucidate to what extent the possible effect could be ascribed to the herbal component alone or if there was a synergistic effect of herbs and vitamins. The null hypothesis was that there was no different effect of Norwegian LV or the herbal component alone as compared to placebo in the prevention of RAU.

Material and methods

Patients
Sixty consecutive patients with minor RAU (Lehner, 1968) were included in the study. The patients were enrolled from the register of patients with RAU at the Faculty of Dentistry, University of Oslo, from colleagues, and among patients who contacted the Department of Oral Surgery and Oral Medicine after reading

Table 1 Contents of Norwegian LongoVital per recommended daily dose – three tablets

Vitamins	*Herbal complex base (408 mg)*	*Additives*
Vitamin A (retinyl acetate), 3000 IU	Pumpkin seeds	Dicalciumphosphate
Vitamin D (cholecalciferol), 400 IU	Rosemary leaves	Microcrystalline cellulose
Vitamin E (tocopheryl acetate), 12 IU	Paprika	Talcum
Vitamin C (ascorbic acid), 60 mg	Milfoil flowers	Polyvinylpyrrolidon
Niacin (niacinamide), 20 mg		Lactose
Pantothenic acid (calcium pantothenate), 10 mg		Silicon dioxide
Vitamin B6 (pyridoxine HCL), 2 mg		Magnesiumstearate
Vitamin B2 (riboflavin), 1.8 mg		Vegetable oil
Vitamin B1 (thiamine mononitrate), 1.5 mg		Shellac

about the trial in the national newspaper. A detailed interview of the patients did not reveal any severe physical or psychological illnesses, and oral diseases apart from RAU were absent. The RAU diagnosis was based on disease history and clinical inspection during an introduction period (IP) of 60 days.

The protocol was reviewed and approved by the local ethics committee and oral consent to participate was obtained after written information about the trial. The inclusion criterion was at least one ulcer attack during IP. Patients who had used LV or any other continuous systemic RAU therapy through the preceding 3 months were not included in the study.

The investigation was designed as a clinical, prospective, placebo-controlled double-blind 10-month trial. The patients started with an IP in order to survey their RAU activity. The patients were asked to fill in a daily record of RAU symptoms, and to contact the examiner for objective confirmation of the diagnosis of RAU. After IP the patients started on the 4 months tablet period (TP) succeeded by a 4-month follow-up period (F-UP) in order to evaluate any possible carry-over effect. The patients were randomly divided into three groups: 20 patients who received LV, 20 the herbal component of LV alone, and 20 placebo. The tablets were coated to make them indistinguishable from each other. As the recommended daily dosage of LV is three tablets in the morning, the patients were instructed to take three tablets every morning together with breakfast and to keep a diary of recurrences. They were furthermore encouraged not to make any changes in lifestyle during the study. Special emphasis was made on not to change smoking habits, toothpaste brand and the use of food supplements. If changes were made during the study, the patients were asked to report this in the diary.

Evaluations

Objective

The patients were clinically examined at the start of IP, day 0 (start of TP), day 30, 120 and day 240. In order to monitor for the effect of the tablets on liver function, blood samples were collected three times: day 0, day 120 and day 240 for determination of the concentration of liver enzymes (alanine transaminase [ALAT], lactate dehydrogenase [LDT] and alkaline phosphatase). Previous studies with the Danish LV showed an immunostimulating effect of the tablets in different patient categories (Pedersen *et al*, 1990b, 1999; B Klausen, LP Ryder, F Nørgaard, A Pedersen, pers. comm.). Therefore, the percentage of T-lymphocyte subsets (CD3+, CD4+, CD8+) and the CD4:CD8 ratio was also determined day 0, day 120 and day 240.

Subjective

Patients registered data for each day on special forms. The registrations included with or without ulcers, ulcer-free days (UFD), number of ulcers (NU), degree of pain, type and amount of alleviating drugs used. The degree of pain was assessed using a numerical scale 1–3, where 1 represented weak pain, 2 moderate pain, and 3 severe pain.

At the clinical examinations, patients were asked about change of general medication, if any illnesses had occurred, possible change in lifestyle, and suspected side effects of the tablets. Patients' period of preference (all-over preference of TP or F-UP when considering degree of pain, number and duration of recurrences, and number of ulcers as a whole) was recorded day 240.

Treatment response

The treatment response was determined from the following parameters:

(1) Number of ulcer-free days (UFD).
(2) Number of new ulcers (NU).
(3) Immunological parameters.
(4) Patients' period of preference.

Statistical methods

Kruskal–Wallis and Mann–Whitney's *U*-test were applied for statistical analysis of intergroup parameters, and Friedman and Wilcoxon's matched-pair signed rank test were used to analyse intragroup parameters. Frequencies were analysed by the sign test (binomial theorem). *P*-values < 0.05 were considered statistically significant.

Results

Eight patients withdrew within the first 4 months of the trial leaving 52 patients for data analysis [32 female (F), 20 male (M); mean age 42 year (range 16–75)]. Further description of the population in Table 2. Eighteen patients had received LV (12F, 6M), 16 the herbal component alone (8F, 8M), and 18 placebo (12F, 6M).

Table 2 Clinical data of the population included in the study - 52 patients with recurrent aphthous ulceration (RAU)

General Background	*n*	*Predisposing Factors for RAU*	*n*	*Previous Treatments*	*n*	*RAU experience*	*n*
Hereditary RAU disposition	36	Mechanical trauma	30	Corticosteroids		Age of onset	
Mild GI complaints	15	Chemical trauma	8	Topical	23	Childhood/teenage	38
Allergic tendencies	20	Food Products		Systemic	4	Adulthood (>20 yr)	14
Often having a cold	11	Citrus	13	Tetracycline rinse	9	Ulcer-Activity	
Daily medication		Tomatoes	4	Chlorhexidine	29	Almost Daily	21
Thyroid hormones	1	Sugar/Chocolate	4	SLS-free toothpaste	44	1-2 recurrence/month	28
Contraceptives	3	Spices	2	Vitamins/Food supplements	15	1 recurrence/2 months	3
Postmenopausal hormones	7	Alcohol	6	Diversified	32	Number of ulcers/recurrence	
Use of vitamins	30	Hormonal changes				1-3 ulcers	41
Herpes labialis	10	Premenstrual	4			>3 ulcers	11
Daily smokers	1	Menopause	1			Duration of ulcers	
Vegetarian	1	Pregnancy	2			1-3 weeks	47
		Colds	14			>3 week	5
		Psychological stress	24				
		Stopped Smoking	8				

None of the treatment-response parameters showed any statistically significant differences between any of the groups at any of the test periods. However, within the LV and the herbal group some differences were demonstrated (Figures 1–3).

Number of ulcer-free days

Within all 3 groups a significant increase in the number of UFD was demonstrated from IP compared to the first 60 days of TP (TP1) (Figure 1). IP median: LV: 16.5; herbs: 13.0; placebo: 14.0, and median of TP1: LV: 20.0; herbs: 21.5; placebo: 22.0. In the LV group, there was a further increase in UFD from the first 2 months to the later 2 months of TP (TP2). TP2 medians: LV: 31.0; herbs: 24.0; placebo: 16.5.

There were no statistically significant differences between any of the three groups from TP as a whole to F-UP. TP median (95% confidence limit of median): LV: 54.0 (16.9–88.9); herbs: 52.0 (10.3–88.6); placebo: 44.5 (17.3–69.1). F-UP medians (95% confidence limit of median): LV: 47.0 (1.4–75.0); herbs: 33.0 (7.2–83.7); placebo 45.0 (21.5–80.9).

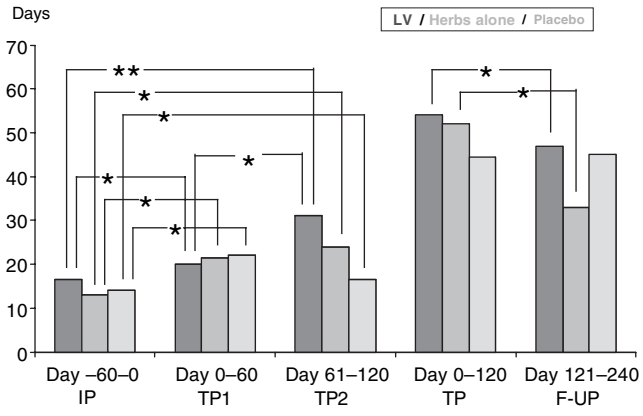

Figure 1 Number of ulcer-free days (medians) during the 2-month introduction period (IP), 4-month daily intake of LongoVital (LV), the herbal component of LV, or placebo (TP), and during the 4-month tablet-free follow-up period (F-UP) in a double-blind trial on 52 patients with minor RAU. Data from TP split up into periods of 2 months are also shown (TP1 and TP2). $^{**}P < 0.01$; $^{*}P < 0.05$. Statistically insignificant differences are not marked

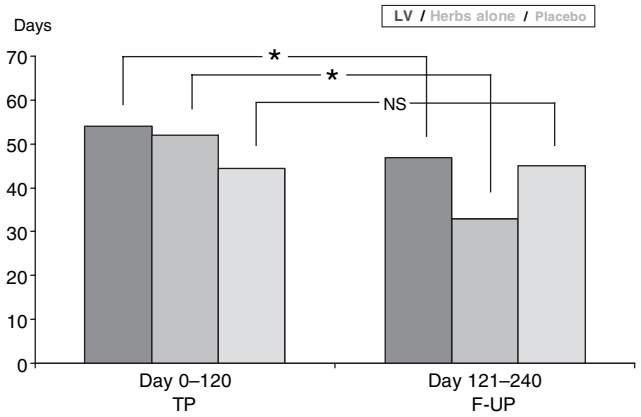

Figure 2 Number of new ulcers (medians) during 4-month daily intake of LongoVital (LV), the herbal component of LV, or placebo (TP), and during the 4-month tablet-free follow-up period (F-UP) in a double-blind trial on 52 patients with minor RAU. $^{*}P < 0.05$; *NS*, not significant

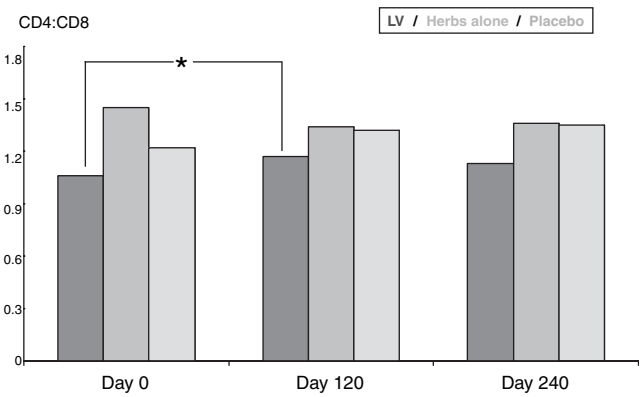

Figure 3 CD4:CD8 ratio (median) during 4-month daily intake of LongoVital (LV), the herbal component of LV, or placebo, and during the 4-month tablet-free follow-up period in a double-blind trial on 52 patients with minor RAU. $^{*}P < 0.05$. Statistically insignificant differences are not marked

Number of new ulcers
There were no statistically significant differences between any of the three groups from TP to F-UP. TP medians (95% confidence limit of median): LV: 12.0 (8.0–28.9); herbs: 23.0 (8.1–28.8); placebo: 13.5 (8.0–22.2). F-UP median (95% confidence limit of median): LV: 9.0 (6.5–14.0); herbs: 15.0 (5.7–24.2); placebo 13.0 (5.9–23.8). Within both the LV and the herbal group, the number of NU was significantly reduced from TP to F-UP (Figure 2).

Liver enzymes
Liver enzyme values were all within or close to the normal ranges at all three times of determination in all three groups. There was no correlation between the type of tablets and liver enzyme values.

Immunological parameters
Neither CD3+, CD4+ nor CD8+ counts showed any significant differences between or within groups at any time. Within the LV group, however, the CD4:CD8 ratio increased significantly from day 0 to day 120 – LV medians (95% confidence limit of median): day 0: 1.06 (0.76–1.96); day 120: 1.17 (0.89–1.98) (Figure 3).

Subjective evaluation of all-over period of preference
There were no significant differences in all-over period of preference between any of the groups.

Reasons for withdrawal from the study
Eight patients withdrew within the first 4 months of the trial – four patients because of problems with indigestion (diarrhoea and/or constipation), one because of pregnancy, one because of an allergic reaction, and two because of lack of time to keep the schedule. Three of the four patients who withdrew because of problems with indigestion withdrew while on herbal tablets and 1 while on LV tablets.

Side effects
Nine of the 52 patients in the study reported mild indigestion problems at the very beginning of the tablet period and they were evenly distributed among the three groups.

Use of alleviating drugs
Alleviating drugs used were mainly topical corticosteroid preparations and different kind of antiseptic mouthwashes. Only one patient had used systemic cortisone twice for a period of 5 days. In the tablet period, alleviating drugs had been used by four patients while on LV, by seven patients while on herbal tablets, and by five while on placebo. In the follow-up period, alleviating drugs had been by two patients in the LV group and by six patients in both the herbal group and the placebo group.

Discussion

In the present study, neither LV nor the herbal component of LV significantly increased the number of UFD or reduced the number of NU compared to placebo. This is in contrast to the former study with the Danish LV where the number of recurrences was significantly reduced after 2 months of intake of LV compared with placebo (Pedersen *et al*, 1990a). The divergent results of the two studies may be explained by the lack of arnica in the Norwegian LV as this is the only major difference between the Danish and the Norwegian LV.

Both within the LV and the herbal group there was a significant reduction in number of NU from the TP compared to F-UP. This supports the previously demonstrated carry-over effect of LV (Pedersen *et al*, 1990a). Considering that the number of NU decreased in F-UP, it is somewhat surprising that the number of UFD decreased in the F-UP.

In the present study, one group received the herbal component alone in order to establish whether the previously demonstrated beneficial effect of LV on RAU was to be ascribed to the herbs alone, or to the combination of vitamins and herbs. No significant differences were demonstrated between LV and the herbal group at any time, suggesting that the benefit of LV on RAU may mainly be assigned to the herbal component.

Several studies with the Danish LV have shown an immunostimulating effect of the tablets in patients with RAU (Pedersen *et al*, 1990b), in patients with Sjögren's syndrome (Pedersen *et al*, 1999), and in periodontal patients (Klausen B, Ryder LP, Nørgaard F, Pedersen A, pers. comm.). In the present study, the CD4:CD8 ratio increased significantly within the LV group only, during the tablet intake. This seems to indicate an immunostimulating effect of the Norwegian LV although not to the same extent as the Danish LV. No changes in any of the evaluated immunological parameters were demonstrated in the herbal group. Thus, the influence of LV on the immune system is possibly caused by a synergism between vitamins and the various trace elements in the herbs (Chandra and Newberne, 1977).

In contrast to the former study with the Danish LV in the treatment of RAU (Pedersen *et al*, 1990a) there were no significant differences in all-over period of preference between any of the groups in the present study.

As in the previous study with LV on RAU (Pedersen *et al*, 1990a), liver enzyme values did not indicate any negative effect on the liver of any of the three different tablets.

The use of toothpaste without the anionic detergent, sodium lauryl sulphate (SLS), has been reported to be of benefit in controlling RAU (Herlofson and Barkvoll, 1994, 1996; Chahine *et al*, 1997). In the present study there was an even distribution of patients using SLS-free toothpaste among the three groups, and the patients were told not to change toothpaste brand during the study periods. Hence, this parameter does not appear to have had any influence on the test results.

In the present study, four patients on LV or the herbal component withdrew from the trial due to indigestion problems. Withdrawals because of side effects have not

been reported in any of the former studies with LV (Pedersen *et al*, 1990a, 1999c; Pedersen, 2001; Klausen B, Ryder LP, Nørgaard F, Pedersen A, pers. comm.). This may indicate that the herbal composition of the Norwegian LV may affect digestion more severely than the Danish LV, or be due to differences in the study groups.

In conclusion, neither the Norwegian LV nor the herbal component alone was superior to placebo in the prevention of RAU. The results, however, indicated that there was a trend favouring LV and the herbs to placebo. Therefore, the Norwegian LV could be recommended as an adjunct to other conventional therapies as a preventive measure in RAU patients.

Arnica was part of the Danish LV when the first study on RAU was done and it is known for its immunostimulating properties (Wagner *et al*, 1985; Wagner and Juric, 1991) which could explain the different clinical and immunological findings in the Danish and the present RAU study. Thus, in order to establish the importance of arnica in RAU prevention, future studies with arnica containing food supplements are awaited with great interest.

Acknowledgement

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References

Axell T (1976). A prevalence study of oral mucosal lesions in an adult Swedish population. *Odont Revy* **27** (suppl 36)**:** 103.

Chahine L, Sempson N, Wagoner C (1997). The effect of sodium lauryl sulphate on recurrent aphthous ulcers: a clinical study. *Compend Contin Educ Dent* **18:** 1238–1240.

Chandra RK, Newberne PM, eds. (1977). *Nutrition, immunity and infection. Mechanisms of interaction*. Plenum Press: New York.

Herlofson BB, Barkvoll P (1994). Sodium lauryl sulphate and recurrent aphthous ulcers. A preliminary study. *Acta Odontol Scand* **52:** 257–259.

Herlofson BB, Barkvoll P (1996). The effect of two toothpaste detergents on the frequency of recurrent aphthous ulcers. *Acta Odontol Scand* **54:** 150–153.

Lehner T (1968). Autoimmunity in oral diseases with special reference to recurrent oral ulceration. *Proc R Soc Med* **61:** 515–524.

Pedersen A (2001). LongoVital® and herpes labialis: a randomised, double-blind, placebo-controlled study. *Oral Dis* **7:** 221–225.

Pedersen A, Hougen HP, Klausen B, Winther K (1990a). LongoVital® in the prevention of recurrent aphthous ulceration. *J Oral Pathol Med* **19:** 371–375.

Pedersen A, Klausen B, Hougen HP, Ryder L, Winther K (1990b). Immunomodulation by LongoVital® in patients with recurrent aphthous ulceration. *J Oral Pathol Med* **19:** 376–380.

Pedersen A, Gerner N, Palmvang I, Høier-Madsen M (1999). LongoVital® in the treatment of Sjögren's syndrome. *Clin Exp Rheumatol* **17:** 533–538.

Wagner H, Juric K (1991). Immunologic studies of plant combination preparations. In- vitro and in-vivo studies on the stimulation of phagocytosis. *Arzneimittelforsch* **41:** 1072–1076.

Wagner H, Proksch A, Riess-Maurer I *et al* (1985). Immunostimulating action of polysaccharides (heteroglycan from higher plants). *Arzneimittelforsch* **35:** 1069–1075.