LongoVital in the prevention of recurrent aphthous ulceration

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LongoVital (LV) (DK. Reg. No. 5178/75) is a herbal based tablet enriched with recommended doses of vitamins. The present study was undertaken to investigate prevention of recurrent aphthous ulceration (RAU) during 6 months' daily intake of LV as compared with placebo in a double-blind, randomized clinical, cross-over 1-yr study. The population comprised 29 otherwise healthy minor RAU patients (18 F, 11 M), mean age 36 (18–67), with an estimated average number of recurrences the previous year of 12.8 (3–30). The number of recurrences was significantly reduced on LV the latter 4 of the 6 months ($P < 0.01$) where 31% were totally free of recurrences. Subjective all-over evaluation of treatment period was significantly in favor of LV. LV induced no adverse reactions and is the first harmless systemic treatment which has proved better than placebo in the prevention of RAU.

Key words: aphthae; herbs; LongoVital; mouth, diseases; prophylaxis; stomatitis; vitamins.

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The etiology of recurrent aphthous ulceration (RAU) remains unknown, and therefore the spectrum of suggested symptomatic therapies is wide (recently reviewed by SCULLY & PORTER (1)). However, the superiority of one to the others is dubious, and so far no systemic modality is known to prevent recurrences. LongoVital (LV) (DK. Reg. No. 5178/75) is a tablet based on dried and ground herbs from pumpkin seeds, arnica flowers, rosemary leaves, paprika and milfoil flower. Furthermore, the nationally recommended doses of vitamins are added to the tablet (Table 1). LV is sold as a food supplement, and beneficial effects of the tablet have so far only been known from case reports. Amongst these, volunteers uninvitedly reported improvement of previously experienced RAU during daily intake of LV for several months. The present study was therefore undertaken in order to investigate possible prevention of RAU during 6 months' daily intake of LV.

Material and methods

The population consisted of 29 patients with minor RAU (2) (18 F, 11 M), mean age 36 yr (18–67). Apart from one woman suffering from myxedema, systemic diseases as well as extraoral manifestations along with RAU were absent. Further description of the population in Table 2. Objectively, all patients appeared to be in physical and psychologic good health, and oral diseases apart from RAU were absent. No subject was accepted for the trial unless RAU had been confirmed by previous objective examination of oral lesions. The protocol was reviewed and approved by the local ethics comittee, and oral consent to participate was obtained after written information about the trial. Thirty-five consecutive patients with at least 2 recurrences the previous year were included and 31 completed the study. Four patients withdrew within the first 2 months, 2 due to unrelated major surgery, and 2 due to lack of time to keep the schedule. Three of the withdrawals dropped out in the LV period, and 1 during placebo intake. Of the 31 completing the study, 2 had had no recurrences during the study period and were therefore excluded, leaving 29 patients for the data analysis.

The investigation was designed as a clinical, prospective, double-blind, 1-yr cross-over study with the intake of LV for 6 months, and placebo for 6 months in randomized order. A wash-out period was omitted as the study design took into account a potential carry over effect of 60 days (see below). The LV tablets have a characteristic appearance and were therefore coated to make them indistinguishable from the inert lactose, placebo tablets. Boxes containing 3 months' supply were handed out at a time. At the beginning of the trial (day 0), patients were given written instructions to take three tablets every morning together with breakfast and to report recurrences on telephone in order to make an appointment for objective assessment of ulcers. They were furthermore free to use alleviating drugs against ulcers during the trial, and requested to continue vitamin intake if they did so prior to the study.

Parameters of iron (hemoglobin, plasma iron, serum ferritin) and vitamin B status (vitamin B_{12}, erythrocyte and plasma folic acid) as well as liver enzymes (alanine transaminase (ALAT), lactate dehydrogenase (LDH), alkaline phosphatase) and C1-esterase inhibitor were determined on day 0, 60, 180, 240 and 360.

Evaluation

Objective – Patients reported recurrences for objective examination. Number and size of ulcers were then recorded by the same investigator (AP) once a week until healing.

Subjective – On special forms, patients registered dates of debut and cessation of symptoms, and the degree of pain was marked once every day on a 100 mm horizontal visual analogue

Table 1. Contents of LongoVital per recommended daily dose – 3 tablets

Vitamins		Herbal complex base (420 mg)	Additives
Vitamin A (retinyl acetate)	3000 iu	Pumpkin seeds	Calciumgluconate
Vitamin D (cholecalciferol)	400 iu	Rosemary leaves	Polyvidonium
Vitamin E (tocopheryl acetate)	12 iu	Paprika	Talc
Vitamin C (ascorbic acid)	45 mg	Milfoil flowers	Lactose
Niacin (niacinamide)	20 mg	Arnica flowers	Magnesiumstearate
Pantothenic acid (calcium pantothenate)	10 mg		Methylcellulosum
Vitamin B_6 (pyridoxine HCl)	2 mg		Cellulosum microcrystal
Vitamin B_2 (riboflavin)	1.8 mg		Shellack
Vitamin B_1 (thiamine mononitrate)	1.5 mg		Siliciidioxidum

scale. The left end of the scale indicated "no pain" and the right end "unendurable pain". After healing of ulcers patients were inquired about use of local and/or general medication, degree of pain compared with previously experienced recurrences, and possible effects of the tablets. On day 60, 180, 240, and 360 the patients were asked about any experienced side effects, and at the final evaluation (day 360) the overall preference period was recorded.

Treatment response – Treatment response was determined from the following criteria: 1) number of RAU recurrences, 2) duration of lesions, 3) number of days with subjective symptoms from RAU, 4) subjective pain recordings, and 5) subjective evaluation of all-over preference period.

Statistical analyses

The Wilcoxon matched-pair signed rank test was applied for analysis of intragroup parameters, and intergroup parameters were analysed by the Mann-Whithey U-test. Frequencies were analysed by the sign test (binomial theorem). *P*-values below 0.05 were considered significant.

Results

Before breaking the trial code, data were analyzed for the whole population without taking the order of treatment into consideration. After the code was broken, it appeared that 13 patients had had LV during the first 6 months (Group A) and 16 LV during the latter 6 months (Group B). Figures on the various parameters in GrA indicated a sustained effect of LV lasting throughout the 6 months' placebo period. Data analysis disregarding the order of treatment was therefore considered inappropriate as differentiation between carry-over effect and any possible effect of time would be impossible. Hence we determined to perform further data analysis on GrA respectively GrB separately. A sustained effect of LV was acknowledged if statistical significant differences were demonstrated within GrB but not in GrA.

Objective parameters

Number of recurrences – Disregarding treatment order ($n=29$), the average number of recurrences was significantly reduced with 39% the latter 4 of the 6 months on LV as compared with placebo ($\bar{x}=1.6$ resp. 2.6; $P<0.01$). In Gr. B the number of recurrences was reduced with 40% during the last 4 months on LV (Table 3). No significant reduction was demonstrated in Gr. A. When, however, applying the non-paired statistics, Gr. A had significantly less recurrences the latter 4 months with LV as compared with placebo in Gr. B ($P<0.05$). Four patients in Gr. A (31%) and five in Gr. B (31%) were RAU free during the last 4 months of LV intake. The number of patients with the less recurrences during the 6 months with LV was statistically significant in Gr. B ($P<0.05$) but not in Gr. A (Table 4). A sustained effect was demonstrated when comparing the expected number of recurrences with the observed numbers during the 6 months with placebo in Gr. A ($P<0.01$) (Table 5).

Duration of recurrences/total number of days with subjective symptoms – The mean duration of recurrences was reduced significantly with 24% on LV in Gr. B ($P<0.05$) (Table 6). The mean duration with placebo in Gr. B was 16.9 days and in Gr. A 8.3 days. This 51% reduction was, however, not statistically significant. The total number of days

Table 2. Characteristics of the study population – 29 minor RAU patients

General background	*n*	Predisposing factors to RAU	*n*	Previous treatment modalities	*n*	RAU experience	$\bar{x}$	(var.)
Hereditary RAU disposition	15	Psychologic stress	9	Zendium toothpaste	20	Duration	20 yr	(3–41)
Mild gastrointestinal complaints	5	Food products	6	Topical corticosteroids	17	Age of onset	15 yr	(3–48)
Allergic tendencies	19	Hormonal changes		Chlorhexidine	15	Estimated no. of recurrences the previous year	12.8	(3–30)
Often suffering from colds	2	– Premenstrually	6	Tetracycline	3	Maximal no. of ulcers / recurrence	5.7	(1–27)
Smoking	7	– Menopause	4	Vitamins	2	Maximal size of ulcers	7.2 mm	(2–20)
Medicine		– Pregnancy	1	Antihistamins	1	Minimal duration of symptoms/recurrence	7.8 days	(1–30)
– Contraceptives	7	Various		Hormones	1	Maximal duration of symptoms/recurrence	17.9 days	(4–60)
– Postmenopausal hormones	3	– Colds	3	Diversified	21			
– Thyroid hormone	1	– Freezing	1					
Use of food supplements		– Physical pain	1					
– Vitamins	13							
– Various	3							

Table 3. Number of RAU recurrences per month during daily intake of LongoVital (LV) or placebo in double-blind, cross-over 1-yr trial on 29 patients with minor RAU.

	Group A				Group B			
	$n=13$				$n=16$			
	LV		Placebo		Placebo		LV	
Period (days)	0–60	61–180	181–240	241–360	0–60	61–180	181–240	241–360
$\bar{x}$	0.90	0.38	0.55	0.50	0.65	0.75	0.65	0.45
Range	0–2.00	0–1.25	0–1.50	0–1.50	0–1.50	0–2.75	0–2.50	0–2.00
	**						*	
Wilcoxon	NS				NS			
		NS					**	
Mann-Whitney		*						

NS not significant; *$P<0.05$; **$P<0.01$

with subjective symptoms per month was lower in the LV periods, but the differences were not significant (Table 7). In Gr. A, however, the 46% reduction from the first 2 to the latter 4 months on LV was statistically significant ($P<0.01$).

Number of ulcers per recurrence/maximum size of ulcers – In Gr. A, the mean number of ulcers per recurrence was not significantly different in the two treatment periods ($\bar{x}=2.0$, range 0–8 on LV; $\bar{x}=1.5$, range 0–4 on placebo). The 42% reduction in Gr. B from a mean of 3.1 (range 0–12) in the placebo period to 1.8 (range 0–6) with LV also was not statistically significant. The maximal measured size of ulcers was reduced with 36% in Gr. B, but this difference was not statistically significant (Table 8). In GrA, however, maximum size of lesions was significantly lower in both treatment periods as compared with the placebo period in GrB.

Table 4. Treatment period with the less recurrences during daily intake of LongoVital (LV) or placebo in double-blind, cross-over, 1-yr trial on 29 patients with minor RAU.

	LV	Placebo
Group A[1] ($n=13$)	5	7
Group B[2] ($n=16$)	10*	2

[1] LV in the first period; [2] LV in the second period; *$P<0.05$, sign test.

Pain score – Neither average nor maximal pain recordings (VAS-scale) were statistically significantly reduced with LV in any of the two treatment groups. In Gr. A, however, a significant 33% reduction in maximal registered pain had taken place from the first 2 months ($\bar{x}=48$ mm) to the latter 4 months on LV ($\bar{x}=32$ mm, $P<0.05$).

Subjective evaluations

All-over preference – Four patients had no period of preference, 18 preferred the LV period and 7 the placebo period ($P<0.05$) (Table 9). In Gr. A there was an even preference but in Gr. B, 12 out of 13 preferred LV ($P<0.01$). The lacking preference of LV in Gr. A substantiates the carry-over effect as 6 of the 7 patients preferring placebo had had LV in the first period.

Relationship between "period of preference" and number of recurrences – A significant concordance was demonstrated between period of preference and number of recurrence as the mean number of recurrences in the preferred period was 2.0 (range 0–7), and 3.4 (range 1–9) in the period without preference ($P<0.01$, Wilcoxon). Twenty patients preferred the period with the less registered number of recurrences, and 5 the period with the more recurrences ($P<0.01$, Sign test).

General discomfort/use of analgesics/local treatment – Eight patients reported general discomfort associated with RAU recurrences during placebo intake, only one during LV intake ($P<0.05$). Three of the patients had used analgesics against pain from ulcers, one in the LV period, and two in the placebo period. Local treatment modalities were used by three patients during LV intake and five during placebo intake.

Table 5. Expected and observed number of RAU recurrences during daily intake of LongoVital (LV) or placebo in double-blind, cross-over, 1-yr trial on 29 patients with minor RAU.

	Group A			Group B		
	$n=13$			$n=16$		
	Expected[1]	Observed		Expected[1]	Observed	
Period (days)		0–180	181–360		0–180	181–360
$\bar{x}$	6.9	5.0	4.8	6.1	5.0	3.5
Range	2.5–25	0–25	0–25	1.5–15	0–13	0–13
Wilcoxon		**	NS		NS	*
		**			**	

[1] Estimated number the previous year divided by 2; NS not significant; *$P<0.05$; **$P<0.01$.

Hematologic parameters

At the beginning of the trial, five patients (three in Gr. A, and two in Gr. B) had hematinic deficiencies. One patient was low in both erythrocyte folic acid and serum ferritin, two were deficient in plasma iron, one in erythrocyte folic acid and one in serum ferritin. Hemoglobin was above normal range in three patients. A few hematologic parameters changed during the 6 months' intake of LV/placebo. The most striking feature was a significant increase in plasma iron during the 6 months' LV intake on 20% ($\bar{x}=16.3$ mmol/L resp. 19.6; $P<0.01$) in Gr. A and on 18% ($\bar{x}=16.7$ resp. 19.7; $P<0.01$) in Gr. B.

A significant, however slight decrease on 4% in hemoglobin was demonstrated during the LV period in Gr. A ($\bar{x}=8.9$ mmol/L resp. 8.5; $P<0.01$) but not in Gr. B ($\bar{x}=8.7$ resp. 8.4). In Gr. A vitamin B_{12} increased significantly during the 6 months *after* LV ($\bar{x}=350$ pmol/L resp. 411; $P<0.05$), and in Gr. B, an increase, however not significant, took place *during* LV intake ($\bar{x}=378$ resp. 389). Erythrocyte folic acid increased significantly during LV intake in Gr. A ($\bar{x}=0.58$ mmol/L resp. 0.67; $P<0.05$), but not in Gr. B ($\bar{x}=0.68$ resp. 0.64), where plasma folic acid decreased during LV intake ($\bar{x}=14.1$ nmol/L resp. 11.4; $P<0.05$).

At the beginning of the trial, 10 patients had liver enzyme values below the normal range (8 were low in ALAT, one in LDH and one in alkaline phosphatase), and 4 above (2 high on LDH and 2 on alkaline phosphatase) whereas C1-esterase inhibitor was above the normal range in 10 patients and low in one patient. At the end of the trial, C1-esterase inhibitor was above the normal range in 5 patients and below in one. Liver enzyme values were below normal range in two patients (one in ALAT and one

Table 6. Duration of RAU recurrences[1] (days) during daily intake of LongoVital (LV) or placebo in double-blind, cross-over, 1-yr trial on 29 patients with minor RAU.

	Group A		Group B	
	$n=12$[2]		$n=15$[2]	
	LV	Placebo	Placebo	LV
Period (days)	0–180	181–360	0–180	181–360
$\bar{x}$	7.9	8.3	16.9	12.9
Range	0–15.6	0–25.0	0–80.0	0–52.3
Wilcoxon	NS		*	

[1]Total number of days with subjective symptoms divided by number of recurrences; [2]1 person in each group excluded due to constant overlap of new recurrences; NS not significant; $P<0.05$.

in alkaline phosphatase) and above in one patient (alkaline phosphatase).

Adverse effects

No unwanted side effects by LV was experienced by any of the patients, but one male felt that his beard had started to grow faster in the LV period. Objectively, no adverse effects were registered.

Subsequent follow-up

The pronounced carry-over effect demonstrated in the blind study, was confirmed by telephone interviews after discontinuation of the trial. In Gr. B, 8 patients (50%) were free of RAU recurrences for 3 months. Of the whole population, 14 of 20 (70%) were either RAU free or had experienced a "certain change for the better" in a period of 8 months after withdrawal of LV.

Discussion

LongoVital is the first harmless systemic treatment which has appeared better than placebo in the management of RAU. Double-blind studies have shown levamisole to be of benefit in RAU prevention in the major part of the studied populations (3–5). However, the reported increase in number of ulcerations in some of the patients (3, 4) as well as the implied risk of general adverse effects (3–5) excludes the use of levamisole in RAU prevention. Besides, recurrence rate is not affected when levamisole administration is restricted to the existence of RAU symptoms (6). With LV, the number of recurrences was significantly reduced the latter 4 of the 6 months' intake in the whole population (disregarding the order of treatment) as well as in GrB. No significant reduction appeared the first 2 months of LV intake. On the other hand, most of the assessed parameters indicated that the favorable effect of LV on RAU recurrences lasted throughout the 6 months' placebo period in GrA. Almost one third of the whole population was recurrence-free over the last 4 months of LV intake. Estimated from the previous year, these patients would be expected to suffer from an average of 2.5 attacks over a 4 months period. It therefore seems most likely to ascribe the absence of ulcers to LV rather than to the fortuitousness of RAU. A placebo controlled trial on systemic zinc sulfate administration for 3 months on 20 minor RAU patients did not show any effect on incidence nor severity of RAU ulcers (7).

In selected groups of RAU patients with hematinic deficiencies, replacement therapy has lead to improvement or remission in 39–87% of the study populations on 28–39 patients (8–10). However, no controlled therapeutic trials on the effect of replacement therapy on RAU incidence have been performed. The five women in the present study who initially had hematinic deficiencies, all responded to the LV intake with less recurrences the latter 4 months compared witht he same period on placebo.

Dietary alterations in selected RAU patients only occasionally reduce ulcer incidence (11, 12). Of 23 patients with an increased histamine release on food antigens, only 30% experienced decreased incidence of ulcers on the elimination of the actual food antigens (10). Our patients were by no means encouraged to change food habits during the study period. A possible food-

Table 7. Number of days with subjective symptoms from RAU per month during daily intake of LongoVital (LV) and placebo in double-blind, cross-over, 1-yr trial on 29 patients with minor RAU.

	Group A[1]				Group B[1]			
	$n=13$				$n=16$			
	LV		Placebo		Placebo		LV	
Period (days)	0–60	61–180	181–240	241–360	0–60	61–180	181–240	241–360
$\bar{x}$	11.5	6.25	8.5	6.25	11.0	10.0	10.0	7.25
Wilcoxon	**		NS		NS		NS	
	*				NS			
	NS				NS			

[1]Range in both periods 0–30 days; NS not significant; $**P<0.01$; $*P<0.05$.

Table 8. Maximum size of ulcers during daily intake of LongoVital (LV) or placebo in double-blind, cross-over, 1-yr trial on 29 patients with minor RAU.

	Group A		Group B	
	$n=13$		$n=16$	
	LV	Placebo	Placebo	LV
Period (days)	0–180	181–360	0–180	181–360
$\bar{x}$	3.4	3.0	7.4	4.7
Range	0–10	0–5	0–25	0–10
Wilcoxon	NS		NS	
			*	
Mann-Whitney			*	

NS not significant; $*P<0.05$.

Table 9. Preference period of 29 patients with minor RAU after daily intake of LongoVital (LV) or placebo in double-blind, cross-over, 1-yr trial.

	LV	Placebo
Group A $n=13$[1]	6	6
Group B $n=16$[1]	12**	1

[1]One patient in group A, and 3 in group B did not have any period of preference; **Significantly different from placebo-preference, $P<0.01$, sign test.

related RAU existed in 6 of the 29 patients. Of these, 5 responded with less recurrences on LV compared with placebo during the latter 4 months. The last patient had had LV in the first period and after the first 2 months of LV intake no recurrences for the remaining study period.

Estrogen and progestogen seem to be beneficial in most females with menstrually related RAU but not in females without such a relationship (13, 14). In the present study, four of the five women, who prior to the trial had experienced a possible reationship between menstrual cycle and RAU, had less recurrences during the last 4 months of LV intake as compared with the same period of placebo intake. The last patient had LV in the first period and experienced no recurrences during the rest of the study period.

In the present study, patients' overall preference was significantly in favor of the LV period. Reliable subjective evaluations were apparently obtained as a significant concordance was demonstrated between period of preference and the period with the least number of recurrences. Of the four patients with no period of preference, three had had LV in the second period. Based on the preference figures in GrA where 6 of the 12 determined patients, preferred the second (placebo) period, it seems likely that a positive LV effect on RAU had not yet penetrated at the time of the final evaluation in three of the four undetermined patients.

No unwanted or unpleasant effects were reported during the LV period. A variety of side effects are quite common on levamisole intake (3–6), occasionally leading to discontinuation of medication (3, 5), and hormone therapy implies the risk of irregular uterine bleeding and amenorrhoea (13, 14).

The hematologic investigations did not indicate any adverse reactions of LV. Some changes in iron parameters and possibly also on B-vitamin status were induced by LV, however, they do not seem to explain the benefit on RAU as an improvement occurred irrespective of lasting low plasma iron in one patient and low erythrocyte folic acid in another patient.

Neither parameters of previous RAU experience nor recurrence rate, duration of recurrences, number and size of lesions during the trial made it possible to separate the patients who did not benefit from LV from the rest of the population. Altogether LV seems to increase the resistance to RAU irrespective of whatever the basic etiology might be. For instance, patients with foodrelated RAU benefited from the treatment on unchanged diet, and females with menstrually related ulcers all responded favorably on LV.

From the mean duration of recurrences with placebo in the first 6 months (16.9 days), it is evident that our population was more severely affected than the average RAU patient in the general population. The very low losses to trial in our study expresses a high degree of motivation which also indicates that the patients suffered quite severely from RAU.

The preventive effects of LV on RAU can most likely be ascribed to the herbal components as the majority of the patients had used vitamins regularly without any experienced effect on the ulcers. If patients before the study used to take vitamins, they were informed to keep on with them during the trial, well knowing that the recommended vitamin doses might then be exceeded in the LV period. If the positive effects of LV should be ascribed the vitamins that would mean that the nationally recommended doses are too low which seems unlikely.

From ancient medicine, the single herbs in the LV tablet are empirically known to exert a variety of clinically effects on the body (15). The mechanism of action of the single herb is, however, not investigated which is unsatisfactory from a scientific point of view. On the other hand, the fact that LV is the first harmless treatment that has proved superior to placebo in the management of RAU should not be ignored.

In conclusion, LV is recommended in the management of RAU. The results indicate that less than 6 months' intake is not advisable, but the apparent sustained effect implies that intermittent therapy with 4 months in between treatments might suffice in most patients to keep ulcer rate at a minimum. However, some patients will probably experience relapse shortly after withdrawal and will thus have to be on permanent treatment. As no adverse reactions were experienced on a 6 months' basis, it seems unlikely that extended periods of intake will imply any risk of side effects.

Criticism may be made on our trial design. The cross-over method was unfortunate as the carry-over effect of LV seemed to last longer than the a priori estimated 2 months. The presented results are therefore mainly based on data from 2 rather small groups of patients, and further investigations on LV in RAU prevention are needed.

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