

Oral supplementation with a nutraceutical containing *Echinacea*, methionine and antioxidant/immunostimulating compounds in patients with cutaneous viral warts

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Aim. The aim of this paper was to determine the effect of oral supplementation (OS) with a nutraceutical, containing methionine, *Echinacea*, zinc, probiotics and other antioxidant and immunostimulating compounds, on the response of cutaneous warts to conventional standard therapy (CST).

Methods. This was an open-label study in adults and adolescents aged 14 years or more and with a body weight ≥ 40 kg, who had at least one cutaneous viral wart. Eligible patients were consecutively allocated to CST (topical therapy with a preparation containing salicylic acid and lactic acid or liquid nitrogen cryotherapy) alone or CST combined with nutraceutical OS for 4 months.

Results. A total of 172 patients were enrolled: 83 received CST alone and 89 CST+OS. During the 6-month observation period, a statistically significant reduction of the mean number of warts was obtained in each treatment group and subgroup. The addition of nutraceutical OS was associated with a significantly lower number of warts at 6 months as compared to CST alone. Complete remission was obtained in 54.5% and 86% of patients in the CST group and CST+OS arm, respectively ($P < 0.001$). The influence of the nutraceutical on the response rate appeared to be more prominent in the subgroup of patients treated with topical therapy. The development of new warts during the study period occurred significantly less frequently with CST+OS compared to CST (9% versus 25%; $P = 0.004$). No adverse events possibly related to the nutraceutical administration were observed.

Conclusion. Our pilot experience seems to suggest that nutraceutical OS is safe and beneficial in patients with cutaneous warts, and capable of enhancing the response to CST.

KEY WORDS: Warts - Cryotherapy - Salicylic acid - Dietary supplements - *Echinacea* - Antioxidants.

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Warts are cutaneous manifestations of human papillomavirus (HPV) which are frequently encountered in clinical practice, especially among children and young adults. Despite of the possibility of spontaneous clearance, natural history, in terms of both remission and recurrence, appears to be unpredictable.¹⁻⁴

Therapeutic management of warts is still a challenge. No single therapy has been proven uniformly and universally effective at achieving complete and stable remission, although many different approaches have been proposed, including combination therapies used to enhance effectiveness.^{3, 4} The two most common treatment modalities for cutaneous warts can be distinguished into patient-applied topical therapies and physician-administered destructive procedures, with the most used ones being represented by topical salicylic acid and cryotherapy with liquid nitrogen, respectively.

Some natural products and oral supplements have been shown to display certain immunoprotective and immunostimulating properties.⁵⁻¹⁰ However, evidence for potential utility of oral nutraceutical sup-

plementation for the treatment of cutaneous warts is lacking. The aim of this pilot experience was to assess the effect of oral nutraceutical supplementation on the response of cutaneous warts to conventional therapy.

Materials and methods

This was an open-label study in adults and adolescents aged 14 years or more and with a body weight ≥ 40 kg, who had at least one cutaneous viral wart. The study followed the ethical principles of the Helsinki declaration and was consistent with good clinical practice guidelines. Patients with plantar warts were excluded as well as those with particularly recalcitrant warts for which alternative treatments were most likely to be required. Other exclusion criteria were immunodeficiency, administration of immunosuppressive drugs, pregnancy, breast-feeding, and hypersensitivity to any ingredients of the study products. Patients entered the study after interruption of anti-wart therapies for at least 4 weeks.

After informed consent, eligible patients were consecutively allocated to one of the following treatment arms: A) conventional standard therapy (CST) alone; B) CST combined with oral supplementation (OS) of a nutraceutical compound (Immuno Skin Plus® tablets, Morgan Pharma S.r.l., Vicenza, Italy), consisting of several antioxidant and immunostimulating substances (methionine, inulin, *Echinacea angustifolia*, *Echinacea purpurea*, probiotics, taurine, vitamin C, coenzyme Q10, vitamin B3, zinc gluconate, and vitamin A). The use of CST was intended to reproduce dermatological practice conditions and modalities, in dependence on the personal experience of each dermatologist, and consisted of liquid nitrogen cryotherapy, with sessions made every 2-4 weeks as needed, or the application once or twice a day of a topical preparation containing salicylic acid 15% and lactic acid 15%. In both treatment arms, CST was continued as appropriate until complete remission was obtained. Study treatment might be interrupted in any time because of inefficacy, adverse events, poor compliance, or any other reason related to the dermatologist's decision or the patient's request.

The nutraceutical OS (1 tablet/day for 20 days per month) was initiated concomitantly with the beginning of the CST and then continued for 4 consecutive months, regardless of the achievement of remission.

TABLE I.—Demographic and general characteristics of the study population.

	CST (N.=83)	CST+nutraceutical (N.=89)
Males/Females	42/41	48/41
Mean age – years (range)	28.2 (14-77)	30.2 (14-67)
History of previous warts (N.)	22 (26.5%)	39 (44%)
Duration of warts (months)	3.9	5.8
Type of CST		
Topical therapy	43	47
Cryotherapy	40	42

CST: conventional standard therapy.

Study assessments were planned at baseline, and after 1, 4 and 6 months, when number and distribution of warts were recorded. Response was graded as complete or partial (with a reduction of at least 50%); reduction less than 50% and progression in the number and/or size of warts were defined as failure. During the observational period the following data were also collected: duration of CST, time to response, development of new warts, adverse events. The last observation carried forward approach was used in case of missing data or premature discontinuations.

Statistical analysis

As concerns statistical analysis, clinical parameters (e.g., total wart count, response rate, number of new warts) within each group were examined using the Wilcoxon test and Chi-square test, whereas the Fisher's exact test, the Mann-Whitney test or the χ^2 tests were used for comparison between groups where appropriate.

Results

The study population comprised 172 patients, 90 males and 82 females, of whom 83 received CST alone (topical therapy N.=43; cryotherapy N.=40) and 89 were treated with CST+OS (topical therapy N.=47; cryotherapy N.=42). General characteristics and demographics are shown in Table I. Patients in the combined therapy group reported more frequently previous episodes of cutaneous warts in their lifetime and tended to have more persistent warts as compared to the group treated with CST alone (Table I). Seven patients were lost to follow-up: 4 in the CST group and 3 in the CST+OS group.

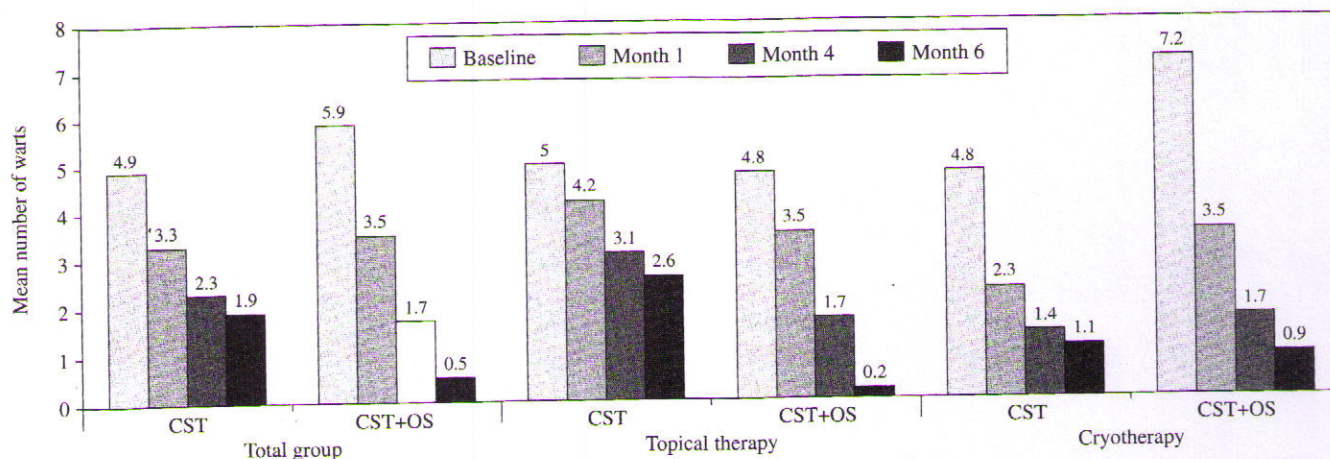


Figure 1.—Change of wart number throughout the study period in patients treated with conventional standard therapy alone (CST) or combined with nutraceutical oral supplementation (CST+OS).

Comparison of the mean number of warts between treatment groups (Figure 1) at baseline has shown the absence of homogeneity since significantly more numerous warts were present prior to the study start in patients allocated to CST+OS as compared to the patients who had to receive CST alone (5.9 versus 4.9; $P < 0.012$). The analysis of subgroups revealed a similar heterogeneity at baseline for patients undergoing cryotherapy (mean total wart number of 7.2 in the combination therapy arm versus 4.8 in patients who were randomized to cryotherapy alone; $P = 0.001$), whereas no significant baseline differences existed in the case of patients who were to receive topical therapy.

During the observation period, a statistically significant reduction of the mean number of warts was obtained in each treatment group and subgroup (Figure 1). The addition of nutraceutical OS was associated with a significantly lower number of warts at 6 months in the total CST+OS group as compared to CST alone. In the subgroups of patients treated with topical therapy, nutraceutical use caused a greater reduction of wart count at 4 and 6 months.

The analysis of response rate (Table II) over the 6-month period documented the achievement of complete remission in 54.5% and 86% of patients in the CST group and CST+OS arm, respectively ($P < 0.001$; χ^2 test). Moreover, the absence of nutraceutical OS was more likely to be associated with treatment failure (37% in CST arm versus 8% in CST+OS arm, $P < 0.001$). The influence of the nu-

TABLE II.—Response rate in the study groups and subgroups (proportion of patients).

	Failure	Partial response	Complete response
CST			
Total group	37%	8.5%	54.5%
Topical therapy	53.5%	9.5%	37%
Cryotherapy	20%	7.5%	72.5%
CST+OS			
Total group	8%	6%	86%
Topical therapy	0	8.5%	91.5%
Cryotherapy	17%	2%	81%

CST= conventional standard therapy; CST+OS= conventional standard therapy combined with nutraceutical oral supplementation

traceutical on the response rate appeared to be more prominent in the subgroup of patients treated with topical therapy. The development of new warts during the study period occurred significantly less frequently with CST+OS compared to CST (9% versus 25%; $P = 0.004$; χ^2 test) and with topical therapy + OS compared to topical therapy alone (2% versus 19%; $P = 0.01$), whereas the difference in proportion of patients with new warts between cryotherapy alone (32.5%) and cryotherapy + OS (15%) did not reach the statistical significance ($P = 0.09$). In patients who obtained complete remission, nutraceutical administration however did not appear to significantly accelerate the response (time to complete remission, 10.5 weeks with CST and 11 weeks with CST+OS,

$P > 0.05$) and did not decrease the mean number of cryotherapy sessions (2.35 for CST and 2.75 for CST+OS), whereas a sensible reduction of the duration of topical therapy was noted in patients who took concomitantly the oral nutraceutical (16 weeks versus 12 weeks in patients treated with topical therapy alone, $P = 0.012$ - Mann-Whitney test).

Adverse events were limited to the occurrence of irritation at the site of application of topical therapy (5/43 in the monotherapy group and 4/47 in the combined therapy group) or liquid nitrogen (5/40 in the monotherapy group and 6/42 in the combination therapy arm). No adverse events possibly related to the nutraceutical administration, including gastrointestinal disturbances or hypersensitivity reactions, were observed.

Discussion

Treatment of cutaneous warts is frequently troublesome and frustrating for both patients and physicians. In the absence of universally effective treatments for cutaneous warts, several therapeutical approaches exist, although the strength of recommendation may be generally rated as weak owing to the low methodological quality of most randomized controlled trials.³ The two most common treatments for cutaneous warts are patient-applied salicylic acid and physician-administered cryotherapy with liquid nitrogen. A recent meta-analysis found sufficient evidence from randomized controlled trials in cutaneous warts to support the efficacy of topical salicylic acid and aggressive cryotherapy.¹¹ The pooled analysis of literature data showed an average cure rate of 23% (5-73%) in placebo trials, 52% (0-87%) in salicylic acid trials, 49% (0-69%) in cryotherapy trials, 54% (45-75%) in aggressive cryotherapy trials and 58% (38-78%) in the combined cryotherapy and salicylic acid trials.¹¹ There is instead insufficient evidence to support the use of other therapies for cutaneous warts. The role of oral nutraceutical in patients with cutaneous warts has been investigated only on very few occasions so far. Some of these studies have evaluated the effect of oral zinc sulfate, showing conflicting results.¹²⁻¹⁵ An open-label study in patients with common or plane warts was aimed at assessing the activity of propolis and *Echinacea purpurea* and demonstrated better results with propolis than placebo or *Echinacea*.¹⁶

In a prospective randomized controlled trial car-

ried out in 262 patients with anal warts the administration of a nutraceutical containing *Echinacea* and other natural products following surgical removal of condylomata was able to significantly reduce the recurrence as compared to patients treated with surgery alone (recurrence rate of 7.2% versus 27.1% in the control group over a follow-up period of 6 months after surgery).¹⁷

The results of our pilot study demonstrate that the administration of a nutraceutical compound, consisting of a multifunctional mixture of substances with antioxidant and immunostimulating properties, may have beneficial effect on the response of cutaneous warts to CST, represented by topical therapy with a keratolytic preparation containing salicylic acid and lactate or liquid nitrogen cryotherapy, according to the dermatologist's preference and experience. The addition of the nutraceutical, for 20 days per month for 4 consecutive months, was able to induce an overall greater reduction of the number of pre-existing and newly developed warts over the 6-month observational period as compared to CST alone.

Moreover, the nutraceutical was found to be safe and well tolerated in our study population.

Conclusions

Despite the limitations of our study, primarily linked to the small sample size, the short follow-up period and the open-label design, these results appear to suggest that nutraceutical OS can be considered as a safe and useful adjunctive tool for the treatment of cutaneous warts. Double-blind randomized placebo-controlled trials with large number of patients and long term follow-up period are however required to obtain definite information.

Riassunto

Supplementazione orale con un nutraceutico contenente Echinacea, metionina e sostanze antiossidanti/immunostimolanti in pazienti con verruche virali cutanee

Obiettivo. Obiettivo del presente studio è stato quello di determinare l'effetto della supplementazione orale (SO) con un nutraceutico, contenente metionina, *Echinacea*, zinco, probiotici ed altre sostanze con proprietà antiossidanti e/o immunostimolanti, nella risposta delle verruche cutanee alla terapia standard convenzionale (TSC).

Metodi. Allo scopo è stato condotto uno studio in aperto

in adulti e adolescenti di almeno 14 anni di età e con peso corporeo minimo di 40 kg, che presentavano almeno una verruca (volgare o piana). I pazienti eleggibili sono stati trattati con TSC (terapia topica con un preparato a base di acido salicilico ed acido lattico oppure crioterapia con azoto liquido) in monoterapia o in combinazione a SO con il nutriceutico per 4 mesi.

Risultati. Sono stati arruolati 172 pazienti: 83 hanno ricevuto TSC da sola e 89 TSC+SO. Durante il periodo di osservazione di 6 mesi, si è osservata una riduzione statisticamente significativa del numero medio di verruche in ciascun gruppo e sottogruppo. L'aggiunta della SO si associava ad un numero significativamente inferiore di verruche al mese 6 rispetto alla TSC in monoterapia. Si è ottenuta la remissione completa nel 54,5% dei casi trattati con TSC e nell'86% dei pazienti del gruppo TSC+SO ($P<0,001$). L'influenza del nutriceutico appariva più pronunciata nel gruppo di pazienti trattati con la terapia topica. Lo sviluppo di nuove verruche durante il periodo di osservazione si verificava meno frequentemente con la TSC+SO rispetto alla sola TSC (9% versus 25%; $P=0,004$). Non si sono osservati eventi avversi potenzialmente correlabili all'uso del nutriceutico.

Conclusioni. Questa esperienza pilota sembra suggerire che la SO con il nutriceutico in oggetto è ben tollerata ed utile nei pazienti con verruche cutanee, potendo potenziare la risposta delle verruche alla TSC.

PAROLE CHIAVE: Verruche - Crioterapia - Acido salicilico - Integratori alimentari - *Echinacea* - Antiossidanti.

References

- Plasencia JM. Cutaneous warts: diagnosis and treatment. *Prim Care* 2000;27:423-34.
- Brodell RT, Johnson SM. Warts: diagnosis and management: an evidence based approach. New York: Martin Dunitz; 2003.
- Gibbs S, Harvey I. Topical treatments for cutaneous warts. *Cochrane Database Syst Rev* 2006;3:CD001781.
- Lipke MM. An armamentarium of wart treatments. *Clin Med Res* 2006;4:273-93.
- Cross ML. Immune-signalling by orally-delivered probiotic bacteria: effects on common mucosal immunoresponses and protection at distal mucosal sites. *Int J Immunopathol Pharmacol* 2004;17:127-34.
- Schoop R, Klein P, Suter A, Johnston SL. *Echinacea* in the prevention of induced rhinovirus colds: a meta-analysis. *Clin Ther* 2006;28:174-83.
- Shah SA, Sander S, White CM, Rinaldi M, Coleman CI. Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis. *Lancet Infect Dis* 2007;7:473-80.
- Paineau D, Carcano D, Leyer G, Darquy S, Alyanakian MA, Simoneau G *et al.* Effects of seven potential probiotic strains on specific immune responses in healthy adults: a double-blind, randomized, controlled trial. *FEMS Immunol Med Microbiol* 2008;53:107-13.
- Overbeck S, Rink L, Haase H. Modulating the immune response by oral zinc supplementation: a single approach for multiple diseases. *Arch Immunol Ther Exp (Warsz)* 2008;56:15-30.
- Nahas R, Balla A. Complementary and alternative medicine for prevention and treatment of the common cold. *Can Fam Physician* 2011;57:31-6.
- Kwok CS, Holland R, Gibbs S. Efficacy of topical treatments for cutaneous warts: a meta-analysis and pooled analysis of randomized controlled trials. *Br J Dermatol* 2011 Jan 11. [Epub ahead of print]
- Al-Gurairi FT, Al-Waiz M, Sharquie KE. Oral zinc sulphate in the treatment of recalcitrant viral warts: randomized placebo-controlled clinical trial. *Br J Dermatol* 2002;146:423-31.
- Sadighha A. Oral zinc sulphate in recalcitrant multiple viral warts: a pilot study. *J Eur Acad Dermatol Venereol* 2009;23:715-6.
- López-García DR, Gómez-Flores M, Arce-Mendoza AY, de la Fuente-García A, Ocampo-Candiani J. Oral zinc sulfate for unresponsive cutaneous viral warts: too good to be true? A double-blind, randomized, placebo-controlled trial. *Clin Exp Dermatol* 2009;34:e984-5.
- Yaghoobi R, Sadighha A, Baktash D. Evaluation of oral zinc sulfate effect on recalcitrant multiple viral warts: a randomized placebo-controlled clinical trial. *J Am Acad Dermatol* 2009;60:706-8.
- Zedan H, Hofny ER, Ismail SA. Propolis as an alternative treatment for cutaneous warts. *Int J Dermatol* 2009;48:1246-9.
- Mistrangelo M, Cornaglia S, Pizzio M, Rimonda R, Gavello G, Dal Conte I *et al.* Immunostimulation to reduce recurrence after surgery for anal condyloma acuminata: a prospective randomized controlled trial. *Colorectal Dis* 2010;12:799-803.