Dermatology Practical & Conceptual

Lip Mesotherapy with Dexpanthenol as a Novel Approach to Prevent Isotretinoin-Associated Cheilitis

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ABSTRACT

Introduction: Isotretinoin (ISO)-associated cheilitis is the most common side effect and the most common reason for discontinuation of ongoing therapy. So, various lip balms are also routinely recommended for all patients.

Objectives: We aimed to investigate the effectiveness of local intradermal injections (mesotherapy) of dexpanthenol into the lips to prevent ISO-associated cheilitis.

Methods: This pilot study was conducted on patients over the age of 18 using ISO (about 0.5 mg/kg/day). All patients were prescribed only hamamelis virginiana distillate in ointment form as a lip balm. In the mesotherapy group (n=28), 0.1 ml of dexpanthenol was injected into each lip tubercle (4 points total) to the submucosal level. The patients in the control group (n=26) used only the ointment. "ISO cheilitis grading scale (ICGS)" was used in the evaluation of ISO-associated cheilitis. The patients were followed for 2 months.

Results: Although there was an increase in ICGS scores in the mesotherapy group compared to the baseline, no statistically significant change was observed after treatment (p=0.545). However, in the control group, there was a statistically significant increase in ICGS scores in the 1st and 2nd months compared to the baseline (p<0.001). Lip balms were needed significantly less frequently in the mesotherapy group compared to the control, both in the 1st and 2nd months (p=0.006, p=0.045; respectively).

Conclusions: Lip mesotherapy with dexpanthenol will be a useful option for preventing ISO-associated cheilitis because of its easy application, cost-effectiveness, low complication risk, and high patient satisfaction.

Introduction

Acne vulgaris is the most common disease in dermatology practice, which can occur at any age, especially in adolescents. Systemic isotretinoin (ISO, 13-cis-retinoic acid) is frequently prescribed for approximately 6-12 months in patients with moderate to severe acne vulgaris, based on a total cumulative dose of 120-150 mg/kg. [1,2] Despite its high efficacy, it has mucocutaneous side effects such as xerosis and cheilitis, which significantly affect the comfort of the patients' life, as well as systemic side effects such as muscle-bone pain, headache, teratogenicity, lipid metabolism, and liver function impairment [1]. Side effects other than teratogenicity are thought to be dose-dependent [2]. Although long treatment duration and side effects are challenging for patients, it is a safe treatment [3]. Severe side effects may lead to dose reduction or termination of treatment. Therefore, it is crucial to control side effects in successful patient management.

ISO-associated cheilitis is the most common side effect caused by treatment-related reduction in sebum production, thinning of the stratum corneum, and changes in the skin barrier [2-4]. The frequency of cheilitis was found to be 77.5% at low doses (0.26-0.50 mg/kg/day) and 96.4% at high doses (0.76-1 mg/kg/day) [2]. It has been reported that the most common cause of patients' ongoing-treatment refusal is cheilitis [2]. So, various lip balms/moisturizers are also routinely recommended for all patients prescribed ISO. The disadvantages of lip moisturizers are their cost, frequent use, and unsatisfactory results. Although vitamin E and omega-3 supplements have been reported to reduce ISO-associated mucocutaneous side effects, they have not been exactly adopted in practice yet [5,6].

Dexpanthenol (D-pantothenyl alcohol, provitamin B5) is frequently used as a topical and localized intradermal microinjection (mesotherapy) in dermato-cosmetology and various diseases. Dexpanthenol moisturizes the skin thanks to its hygroscopic properties and repairs the skin barrier by hydrating the stratum corneum and reducing transepidermal water loss [7]. It has been commonly used as an over-the-counter topical drug for more than 70 years in diseases such as nappy rash, contact dermatitis, seborrheic dermatitis, cracked nipples, especially atopic dermatitis, and dry skin [7]. It supports skin regeneration and wound healing by increasing epidermal differentiation [8]. Also, it reduces inflammation after irritation with its anti-inflammatory properties [9,10]. Allergic reaction due to dexpanthenol is rare, and it is a safe agent [11]. Dexpanthenol may be useful in the prevention and treatment of ISO-associated cheilitis due to these properties.

Objectives

We aimed to investigate the effect of the combination of conventional topical lip balm and lip mesotherapy (dexpanthenol) in the prevention of ISO-associated cheilitis on patient satisfaction, need for moisturizer, and clinical outcomes.

Methods

This study was approved by the Local Ethics Committee (Decision No: 2021/12-186). The study was performed as per the latest version of the Helsinki Declaration and the Guidelines for Good Clinical Practice.

In the study protocol, the aim was not to investigate the superiority of mesotherapy over lip balm, but to evaluate the benefits of combining it with conventional topical care. This pilot study was conducted on patients who received ISO for the first time in Dermatology outpatient clinics between January 2021 and March 2021. Only patients over 18 years using about 0.5 mg/kg/day ISO were enrolled in the study. Written informed consent was obtained from all participants. Exclusion criteria from the study were the following: the presence of atopy, change of dose during follow-up, presence of any rheumatological disease, additional drug use, lip-licking/biting habit, acne excorie, immunodeficiency, local infection, using any steroid cream on the lips and dexpanthenol allergy.

In our practice, we recommend dexpanthenol mesotherapy to the lips in addition to lip balm to all eligible patients using ISO with a proactive approach to reduce the risk of cheilitis or dry lips. We have got quite positive feedback from this procedure, which has a low side effect profile. In this study, we retrospectively evaluated patients with and without dexpanthenol mesotherapy to the lips. We conventionally recommend a lip balm to every patient using ISO, even if lip mesotherapy has been applied. All patients included in the study were prescribed only hamamelis virginiana distillate in ointment form (Hametan® 25% ointment) as a lip balm. None of the patients used any additional product to moisturize their lips.

Firstly, 5% lidocaine pomade was applied to the lips of patients who approved the procedure. After waiting approximately 10-15 minutes, 0.1 ml of dexpanthenol (Bepanthen® 500 mg/2 ml Ampoule with the solution for injection) was injected into each lip tubercle (4 points in total) to the submucosal level (approximately 3-4 mm depth) using a 30 gauge-13 mm needle. During the follow-up with the patients, data such as the pain level of the procedure (Visual Analog Scale (VAS, 0-10 points)), possible side effects such as edema and ecchymosis, subjective satisfaction levels, and effect duration of the treatment were recorded. "ISO cheilitis grading scale (ICGS)" developed by Ornelas et al. was used in the evaluation of ISO-associated cheilitis [5] (Table 1).

All procedures were conducted using Statistical Package for Social Sciences software (SPSS Inc., Chicago, IL, USA, v21.0). After checking the normality distribution of scale

Table 1. Isotretinoin Cheilitis Grading Scale.

	Erythema	Scale/Crust	Fissure	Commissures
0	No involvement	No involvement	No fissures	No involvement
1	Mild erythema	Mild scale/crust	One fissure	Mild involvement: erythematous or scaly
2	Moderate erythema	Moderate scale/crust	Two to four fissures	Moderate involvement: erythematous and scaly, lichenified, mild fissuring
3	Severe erythema	Severe scale/crust	Greater than four fissures	Severe involvement: more extensive erythema, scale, and lichenification or any of those with severe fissuring

Total score: ranges from 0 to 12

Table 2. Comparison of patient characteristics and ISO dose between groups.

		Mesotherapy group (n=28)	Control group (n=26)	p-value
Age, years		23.8 ± 3.2	24.0 ± 3.6	0.917
Sex	Man	9 (32.1%)	10 (38.5%)	0.627*
	Woman	19 (67.9%)	16 (61.5%)	
Baseline ICGS (ranging 0-12 points)		0.6 ± 0.7	0.6 ± 0.7	0.728
Body-mass index (kg/m^2)		22.3 ± 3.4	22.4 ± 2.9	0.890
Daily ISO-dose (mg/day)		29.6 ± 6.4	31.9 ± 4.0	0.142
Daily ISO-dose/kg (mg/kg/day)		0.50 ± 0.06	0.51 ± 0.05	0.141

ICGS: Isotretinoin Cheilitis Grading Scale, ISO: Isotretinoin
Mann Whitney U and Pearson's chi-square* tests were used.

variables by Shapiro Wilks, Wilcoxon and Friedman's tests were used to compare two and more than two dependent groups, respectively. Bonferroni adjustment was applied as post-hoc (Wilcoxon signed-rank tests) after Friedman's test (Bonferroni-adjusted two-sided significance level<0.05). Mann-Whitney U test was used for independent groups. Pearson's chi-square test was used to compare independent categorical variables.

Results

The study involved 28 patients receiving dexpanthenol mesotherapy (mesotherapy group) and 26 patients without the procedure (control group, ointment only). The groups were identical in terms of age and sex distribution (p=0.917, p=0.627; respectively). The groups were identical for baseline ICGS (p=0.728). All patients were using ISO at a dose of approximately 0.5 mg/kg, and there was no statistical difference between the groups in terms of dosage (p=0.141) (Table 2).

The groups were compared with themselves and each other for the ICGS scores and frequencies of daily use of lip balm during the 2-month follow-up period (Table 3). In the mesotherapy group, despite the ISO treatment, although there was an increase in ICGS scores compared to the baseline, no statistically significant change was observed (p=0.545). However, there was a statistically significant increase in ICGS scores at the 1st and 2nd months of ISO treatment in the control group compared to the baseline (p<0.001). While there was no difference between the groups in terms of ICGS scores at baseline, there was a statistically significant difference at both 1 and 2 months (both, p<0.001) (Figure 1). The daily need for lip balm increased significantly in both groups compared to the baseline (both, p<0.001). However, in the mesotherapy group, lip balms were needed significantly less frequently compared to the control group both in the 1st and 2nd months of ISO treatment (p=0.006, p=0.045; respectively). As seen in Table 3, the patients had high satisfaction rates from dexpanthenol mesotherapy, and a statistically significant increase was observed in the satisfaction rates after the 2nd session (p=0.005). According to 96.4% (n=27) of the patients, the effect of mesotherapy appeared in only 1-2 days. After two mesotherapy sessions, it was observed that the patients' opinions about the effect duration of the treatment had altered. The effect duration was more than four weeks according to 26.1% of the patients, and 2-4 weeks according to 34.8%-65.2% of them. In the follow-up with the patients, mild angular cheilitis was observed in 3 (10.7%) patients in the mesotherapy group.

The mean score of the procedure-related pain after topical anesthesia was 4.1±1.1. No additional complications were observed.

Table 3. Comparison of several parameters with dependent and independent groups.

		Baseline	1st month	2nd month	*p-value* *
Grade score of ISO-associated cheilitis (ranging 0-12 points)					
Mesotherapy group (n=27)		0.6 ± 0.7	1.1 ± 1.3	0.8 ± 0.7	0.545
Control group (n=26)		0.6 ± 0.7	2.8 ± 0.7	3.4 ± 1.5	**<0.001**[a,b]
	p-value **	0.728	**<0.001**	**<0.001**	
Frequency of daily use of lip balm (hamamelis ointment)					
Mesotherapy group (n=27)		0.9 ± 0.5	4.7 ± 2.3	4.3 ± 2.4	**<0.001**[a,b]
Control group (n=26)		0.8 ± 0.7	6.0 ± 2.5	6.9 ± 4.6	**<0.001**[a,b]
	p-value **	0.597	**0.006**	**0.045**	
The patients' opinions in the mesotherapy group regarding the treatment					
Satisfaction level (n=23)	Very satisfied	-	7 (30.4%)	13 (56.5%)	**0.005**
	Satisfied	-	14 (60.9%)	10 (43.5%)	
	Slightly satisfied	-	2 (8.7%)	0 (0.0%)	
	Unsatisfied	-	0 (0.0%)	0 (0.0%)	
Effect duration (n=23)	≥4 weeks	-	6 (26.1%)	6 (26.1%)	0.106
	2-4 weeks	-	8 (34.8%)	15 (65.2%)	
	≤2 weeks	-	9 (39.1%)	2 (8.7%)	

Data are expressed as mean ± standard deviation.
* Wilcoxon and Friedman's tests were used for comparisons of two and more than two dependent groups, respectively. Bonferroni adjustment was applied as post-hoc (Wilcoxon signed-rank tests) after Friedman's test (Bonferroni-adjusted significance level<0.05).
** Mann Whitney U test was used for independent groups.
a: p<0.05 for the difference between baseline and 1st month; b: p<0.05 for the difference between baseline and 2nd month; c: p<0.05 for the difference between 1st month and 2nd month in 2-month patient follow-up

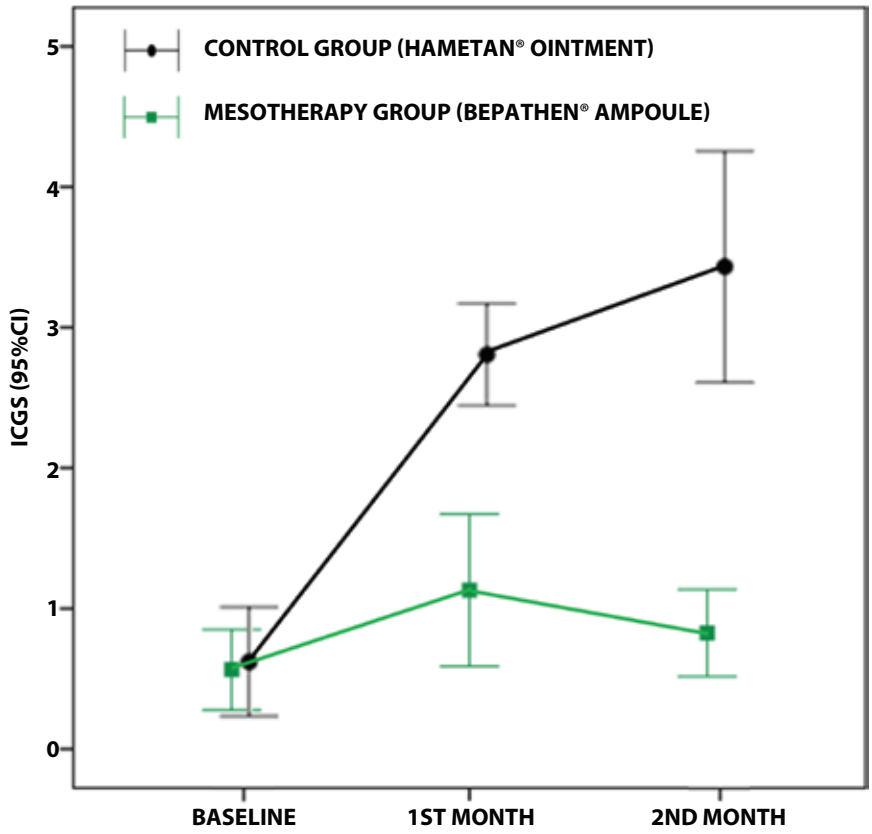

Figure 1. ISO-associated mucositis was significantly lower in the mesotherapy group than in the control group both at 1st month and 2nd months when compared by ICGS scores.
ICGS: Isotretinoin cheilitis grading scale, CI: Confidence interval.

Conclusions

Cheilitis is characterized by erythema, dryness, crusting, fissures, and inflammation of the commissures on the lips. It greatly affects the quality of life of patients due to burning, itching, and edema [5]. Various sub-clinical types of cheilitis can be encountered secondary to different etiological factors such as actinic damage, systemic diseases, immunosuppression, nutritional deficiencies, local irritants and allergens, infections, and drugs [9,10]. The main cause of drug-associated cheilitis is systemic retinoids [10]. ISO is an indispensable and safe agent of dermatology practice with high cure rates for acne vulgaris [1]. However, it should not be overlooked that ISO-associated cheilitis is the leading cause of early termination of treatment, with a rate of 1.4% [2]. Effectively reducing the risk of cheilitis will increase patient comfort and treatment sustainability. Although various supplements such as vitamin E, omega 3, and primrose oil have been recommended in some studies for mucocutaneous side effects, there is no established treatment method other than moisturizers [6,11,12]. In randomized controlled studies, it was reported that vitamin E supplementation did not significantly reduce the xerosis associated with ISO [13,14]. Patients may not be willing to use another systemic therapy while also undergoing long-term ISO therapy. Therefore, we consider it to be challenging to use oral supplements in practice. We introduce lip mesotherapy with dexpanthenol as a novel approach.

We have experienced highly satisfactory results with lip mesotherapy with dexpanthenol, which has a high safety profile and which we frequently prefer in indications such as hair loss, wound healing, and rejuvenation. To the best of our knowledge, the effectiveness of dexpanthenol in lip mesotherapy has not been reported so far. In this study, we found that dexpanthenol mesotherapy combined with topical therapy has excellent efficacy in preventing ISO-associated cheilitis. While there was no difference between the groups in terms of the severity of baseline cheilitis and the frequency of lip balm use before treatment, both parameters were lower in the mesotherapy group compared to the control group in both 1st and 2nd-month examinations. However, even if mesotherapy is performed in patients using ISO, topical care should be offered to every patient due to the significant increase in the need to use lip balm. The clinical results recorded in the follow-up of the patients in the mesotherapy and control groups after ISO were presented in Figure 2 and Figure 3, respectively.

It is assumed that mesotherapy allows slower diffusion, higher levels, and longer-lasting effects of drugs in the tissues around the injection site compared to intramuscular injection or topical applications [15]. This method is a safe transdermal drug delivery tool applied by injecting vitamins, minerals, and various bioactive substances into the skin layers to stimulate fibroblast activity and collagen genesis and reverse elastin degeneration and transepidermal water loss [15,16]. Patients may experience injection-related side effects such as pain, erythema, edema, and ecchymosis. Only one of the patients in the study hesitated to continue treatment because of pain. The patients stated that they had no experience of any bruising or ongoing pain after the procedure and that the edema on the lips usually regressed within 1-2 hours. Mild-moderate pain was noted despite topical anesthesia. We think that this may be reduced further by adding lidocaine solution to dexpanthenol. Since we observed angular cheilitis in some patients, although the vermilion was normal, we concluded that 0.05-0.1 ml dexpanthenol mesotherapy to the lip commissures, in addition to 4-point injection, would yield better clinical results. The satisfaction rates of the patients were high, and the significant increase

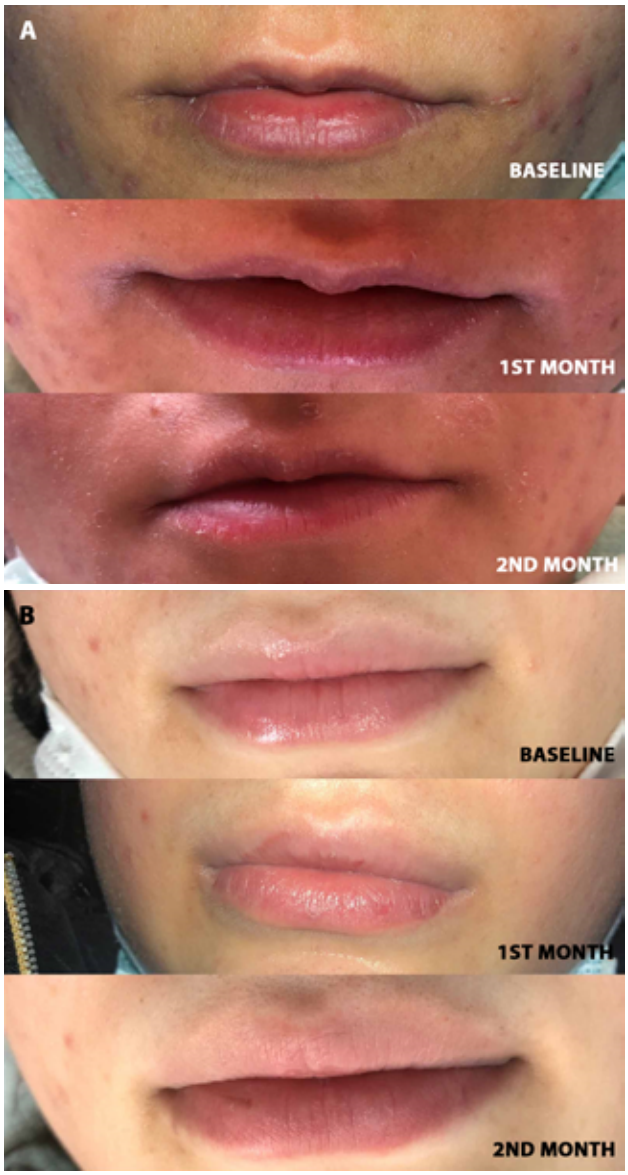

Figure 2. Patients administered with dexpanthenol mesotherapy to the lips.

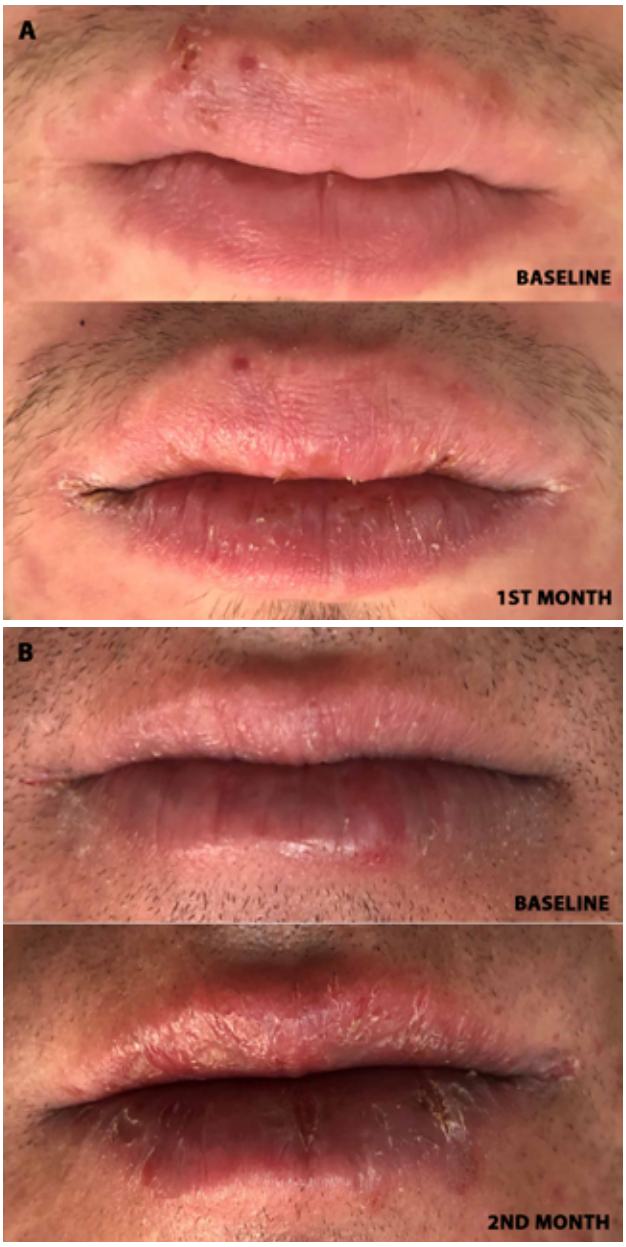

Figure 3. Control patients applying hamamelis ointment to the lip.

in the satisfaction rates after the second session was remarkable. It has been claimed that the most disturbing period in ISO-associated cheilitis is the first month of treatment, after which patients adapt to xerotic changes [11]. The increase in the satisfaction levels of the patients after the second session may be related to this adaptation process.

Dexpanthenol is an important molecule for the physiological function of the epithelium. After absorption through the skin, it quickly turns into pantothenic acid, a component of coenzyme-A.[11,17] Coenzyme-A is an essential cofactor in the metabolism of carbohydrates, fatty acids, sphingolipids, proteins, sterols, and steroid hormones [12]. Dexpanthenol interacts with the relevant lipid and protein molecular segments in the corneocytes, thus increasing the hydration of the skin by contributing to molecular fluidity [17,18]. Studies have demonstrated the migration, proliferation, and gene regulation effects of dexpanthenol on dermal fibroblasts [8,19,20]. We think dexpanthenol injected into the submucosa reduces the severity of cheilitis and the need for moisturizer by increasing hydration and regeneration in ISO-damaged skin, reducing irritation. There are limited studies comparing the efficacy of mesotherapy compared to topical applications of the same agent. While there is no research on the efficacy of dexpanthenol, submucosal injection of vitamin C in gingival hyperpigmentation has been found to be superior to the use of its topical form [21].

Although the main limitation is a small sample size, statistically significant high efficacy rates were achieved. Transepidermal water loss measurement was not included in the protocol due to technical impossibility. The shortcoming of the study was that we could not compare dexpanthenol mesotherapy with the topical form of dexpanthenol and placebo. The non-reimbursement of dexpanthenol ointment and the excessive diversity of similar products on the market necessitated the use of hamamelis virginiana as a control group in our retrospective study. Because hamamelis virginiana (Hametan® ointment), an alternative to dexpanthenol, is one of the most frequently preferred reimbursed medical products in our country. Indeed, Wolff and Kieser investigated the clinical effects of ointment forms of hamamelis and dexpanthenol in the treatment of skin/mucous membrane inflammation in children [22]. Accordingly, physicians' and parents' efficacy assessments revealed similar or better treatment ratings of hamamelis ointment than dexpanthenol. While it is plausible that water intake reduces the mucocutaneous side effects of ISO, there is no evidence to our knowledge. Therefore, water intake is lacking in the study protocol.

In conclusion, the effectiveness of lip mesotherapy with dexpanthenol in the prevention of ISO-associated cheilitis was remarkable. We believe that this method will be a useful adjuvant option for both the prevention and treatment of ISO-associated cheilitis because of its easy application, low cost, low complication risk, and high patient satisfaction. However, patients' opinions and approvals on whether they want such a needle application should be evaluated. Further placebo-controlled, randomized studies with larger sample sizes are needed.

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