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ORIGINAL ARTICLE

Lip mesotherapy with dexpanthenol in the treatment of isotretinoin-induced cheilitis

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Abstract

Introduction: Cheilitis is the most common mucocutaneous side effect of isotretinoin (ISO). Dexpanthenol (DXP) increases fibroblast proliferation and re-epithelialization in wound healing. We aimed to investigate the effect of DXP-mesotherapy in ISO-induced cheilitis in this study.

Methods: This study was conducted on patients who had been using ISO (0.5–1 mg/kg/day) for at least 2 months. Twenty-five patients who administered DXP-mesotherapy (mesotherapy group) and 33 patients without the procedure (control group, only ointment) participated in this study. All patients were prescribed only hamamelis virginiana distillate in ointment form as a lip balm. The efficacy of the treatment was interpreted by the change in lip balm use frequency, quality of life, and Isotretinoin Cheilitis Grading Scale (ICGS).

Results: There was a statistically significant decrease in all ICGS-subgroups scores in the mesotherapy group after 1 month compared with the baseline (p = <0.001), although in the controls, erythema, crust, and fissure scores significantly increased (p = 0.001, p = 0.002).While there was no difference between the groups in terms of ICGS total scores at baseline, there was a significant difference after 1 month in favor of the mesotherapy group ($p < 0.001$). In the mesotherapy group, lip balms were needed significantly less frequently and there was a significant improvement in quality of life compared with both the control group and at baseline after 1 month (both; $p < 0.001$). On the other hand, the control patients suffered more from cheilitis and dryness than at baseline ($p < 0.001$).

Conclusion: Dexpanthenol-mesotherapy seems to be a safe, and so effective method in management of ISO-related cheilitis.

KEYWORDS
cheilitis, dexpanthenol, isotretinoin, lip, mesotherapy

1 | INTRODUCTION

Acne is a chronic, inflammatory skin disease that most commonly affects adolescents. Treatment options vary depending on the severity of acne and the psycho-sociological impact of the disease on the patients.[1] Isotretinoin (ISO), a vitamin A analog, is especially preferred in the treatment of severe acne. ISO affects all the steps of acne pathogenesis and provides satisfactory results in the treatment. However, it has many side effects related to many systems such as hepatic, musculoskeletal, hematological, neuropsychiatric,

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and gastrointestinal systems, most frequently mucocutaneous side effects.[2] The dosage of ISO is 0.5–1 mg/kg/day. Mucocutaneous side effects such as cheilitis and xerosis increase with higher doses of ISO. After administration of ISO, a cumulative dose of 120–150 mg/kg is recommended to increase remission rates and reduce relapses.[3]

Dry lips and cheilitis are the most common (90–100%) mucocutaneous side effects of ISO.[4] The Isotretinoin Cheilitis Grading Scale (ICGS), developed by Orneals et al., is used to objectively evaluate the severity of ISO-related cheilitis (Table 1).[5] ISO-related cheilitis and lip dryness are dose-dependent, predictable, and controllable.[4] Current treatment is based on the use of moisturizing and emollient products to alleviate the symptoms of ISO-related cheilitis.[5]

Dexpanthenol (DXP) is an alcohol derivative of pantothenic acid, a component of B complex vitamins, and an essential component of a normally functioning epithelium.[6,7] DXP is enzymatically degraded to form pantothenic acid in the skin and mucous membranes, and it plays a role in the biosynthesis of glutathione, ATP, and coenzyme A, all of which have a protective effect against cell damage.[7–9] DXP, which has both antioxidant and anti-inflammatory effects, can be used topically and systemically.[6] Dermatological benefits of the topical use of dexpanthenol include increased fibroblast proliferation and accelerated re-epithelialization in wound healing.[6]

In our practice, we have suggested DXP mesotherapy to the lips in addition to lip balm to all patients with ISO-associated cheilitis to improve mucosal complaints. We have been getting positive feedback from patients. This pilot study aims to present our experience with DXP mesotherapy of unknown efficacy in ISO-related cheilitis and to report treatment outcomes in a prospectively followed series of patients.

2 | MATERIALS AND METHODS

2.1 | Ethics

The study protocol was approved by the ethics committee of the Erzurum Regional Training and Research Hospital (reference no. 2021/12-187). An informed consent form was obtained from all participants. The study was performed as per the latest version of the "Helsinki Declaration" and the "Guidelines for Good Clinical Practice."

2.2 | Study design

This study protocol was not designed to explore 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 adult patients who had been using ISO (0.5–1 mg/kg/day) for at least 2 months between July and September 2021 and were still on treatment. Exclusion criteria were the presence of atopy, history of cheilitis before ISO, dose changes during follow-up, the presence of rheumatological disease, additional drug use, lip licking/biting habit, acne excoriation, immunodeficiency, local infection, and use of any steroid, allergy to the cream and dexpanthenol.

Patients with ISO-related cheilitis or dry lips were enrolled in the follow-up form prepared for prospective evaluation, who gave consent to mesotherapy (mesotherapy group) or not (control group). All patients included in the study were prescribed only hamamelis virginiana distillate in ointment form (Hametan® %25 ointment, Abdi İbrahim Pharmaceuticals, İstanbul, Turkey) as a lip balm. None of the patients used any additional product to moisturize their lips. ICGS was used to assess the severity of ISO-related cheilitis. Physicians performing DXP mesotherapy and recording ICGS were different from each other. All patients were re-evaluated by a blind dermatologist in terms of clinical findings the following month. Besides, patients who underwent mesotherapy were questioned in terms of procedure-related side effects such as pain (VAS, 0–10 points), ecchymosis, edema, subjective satisfaction levels, and onset and duration of effect. The effect of cheilitis on quality of life before and after treatment was questioned by VAS. The efficacy of the treatment was interpreted by the change in lip balm use frequency, quality of life, and ICGS. Patient satisfaction and opinions about the procedure were also evaluated.

2.3 | Procedure

First, 5% lidocaine pomade was applied to the patients' lips approving the procedure and waited approximately 15 min. Then, 0.1 ml dexpanthenol (Bepanthen® 500 mg/2 ml Ampoule with the solution for injection, Bayer Pharmaceuticals, İstanbul, Turkey) was injected

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

Note: Total score: ranges from 0 to 12.

into each lip tubercle and near the commissures from a total of 6 different points to the submucosal level (about 3–4 mm depth) using a 31 gauge-4 mm needle.

2.4 | Statistical analysis

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 variables by Shapiro–Wilks, Wilcoxon, and Mann–Whitney *U* test were used for dependent independent groups; respectively. Pearson's chi-squared test was used to compare independent categorical variables.

3 | RESULTS

Twenty-five patients who administered DXP mesotherapy (mesotherapy group) and 33 patients without the procedure (control group, only ointment) participated in this study. The groups were evenly distributed in terms of age and sex. ($p = 0.088$, $p = 1.000$; respectively), and there was no difference for baseline ICGS between the groups ($p = 1.000$). A dose of approximately 0.5–1 mg/kg of ISO was administered to all patients in two groups. There was no statistical difference between the groups in terms of dose ($p = 0.863$), total duration of treatment ($p = 0.648$), and total cumulative dose of ISO ($p = 0.537$) (Table 2).

The changes in the four subgroups constituting ICGS were observed during patient follow-up in the mesotherapy and control groups (Table 3). The groups were compared with themselves and each other for the ICGS subgroups scores. There was a statistically significant decrease in all ICGS scores in the mesotherapy group after a month. Contrary to this, in the control group, it was found that erythema, crust, and fissure, except angular cheilitis, scores were statistically significantly higher after a month compared with the baseline ($p = 0.001$, $p = 0.002$, $p = 0.002$, $p = 0.180$; respectively). While there was no difference between the groups in terms of ICGS total scores at baseline, there was a statistically significant difference after a month in favor of the mesotherapy group ($p < 0.001$) (Table 4) (Figure 1). The daily need for lip balm was similar in both groups at baseline ($p = 0.465$). However, in the mesotherapy group, lip balms were needed significantly less frequently compared with the control group and at baseline, after a month (both, $p < 0.001$) (Table 4). The impact of existing dryness and cheilitis on quality of life at baseline was higher in mesotherapy patients than in the control group ($p = 0.002$). However, after 1 month, there was a significant improvement in quality of life in the mesotherapy group compared with both the control group and at baseline (both, $p < 0.001$). The control patients, on the other hand, suffered more from cheilitis and dryness than at baseline, after 1 month ($p < 0.001$) (Table 4).

As seen in Table 5, the patients had high satisfaction rates from dexpanthenol mesotherapy. The day of improvement after the procedure was ranged 1–7 day (3 ± 1.5). The effect duration was more than 4 weeks according to 20.8% of the patients, and 2–4 weeks according to 50.0% of them. 56% of the patients were willing to undergo dexpanthenol mesotherapy again. In the follow-up of the patient, ecchymosis was observed in 1 (4.0%) patient in the mesotherapy group. The mean score of the procedure-related pain after topical anesthesia was 4.6 ± 1.4 and the duration of procedure-related lip edema ranged between 0.5 and 3 h (4.6 ± 1.4). No additional complications were observed.

While no relationship was found between the desire to continue DXP mesotherapy and the severity of procedure-associated pain, there was a significant relationship with the level of satisfaction ($p = 0.843$, $p = 0.007$; respectively).

TABLE 2 Comparison of patient characteristics and ISO dose between groups

Confounders	Mesotherapy group ($n = 25$)	Control group ($n = 33$)	*p*-value
Age, years	22.4 ± 5.0	20.3 ± 3.1	0.088
Sex			
Man	5 (20.0%)	6 (18.2%)	1.000*
Woman	20 (80.0%)	27 (81.8%)	
Baseline ICGS (ranging 0–12 points)	6.4 ± 1.6	5.4 ± 2.4	0.100
Frequency of daily lip balm use before ISO	0.4 ± 0.5	0.3 ± 0.5	0.481
Body-mass index (kg/m^2)	21.6 ± 3.5	20.9 ± 2.5	0.802
Daily ISO-dose (mg/day)	39.6 ± 4.6	39.4 ± 5.0	0.863
Daily ISO-dose/kg (mg/kg/day)	0.67 ± 0.13	0.70 ± 0.13	0.350
The total duration of treatment (months)[a]	3.8 ± 1.2	4.0 ± 1.4	0.537
Total cumulative dose of ISO (mg)[a]	3900 ± 1509	4106 ± 1686	0.648

Note: Mann–Whitney *U* and Fisher's exact* tests were used.

Abbreviations: ICGS, Isotretinoin Cheilitis Grading Scale; ISO, Isotretinoin.

[a]Calculated according to the date of enrollment in the study.

TABLE 3 The change observed during patient follow-up in the four subgroups constituting ICGS in the patient and control group

Parameters	Groups	Baseline (after ISO)	After a month	*Z* value	*p*-value[a]
Erythema	Mesotherapy	1.8 ± 0.4	1.4 ± 0.5	−3.317	**=0.001**
	Control	1.6 ± 0.7	2.0 ± 0.4	−3.357	**=0.001**
	p-value[b]	0.222	**<0.001**		
Crust	Mesotherapy	1.8 ± 0.5	1.1 ± 0.4	−4.123	**<0.001**
	Control	1.6 ± 0.5	2.0 ± 0.6	−3.232	**=0.002**
	p-value[b]	0.063	**<0.001**		
Fissure	Mesotherapy	1.5 ± 0.7	0.9 ± 0.4	−3.771	**<0.001**
	Control	1.2 ± 0.7	1.5 ± 0.5	−3.162	**=0.002**
	p-value[b]	0.100	**<0.001**		
Angular cheilitis	Mesotherapy	1.3 ± 0.8	0.8 ± 0.7	−3.606	**<0.001**
	Control	1.1 ± 0.7	1.2 ± 0.6	−1.342	0.180
	p-value[b]	0.465	**0.013**		

Abbreviation: ISO, Isotretinoin.

[a]Wilcoxon test was used for comparisons of two dependent samples.

[b]Mann–Whitney *U* test was used for independent samples.

Bold indicates statistical significant value ($p<0.005$).

TABLE 4 Comparison of several parameters with dependent and independent group analyses

	Baseline (after ISO)	After a month		
ICGS (ranging 0–12 points)			*Z* value	*p*-value[a]
Mesotherapy group ($n = 25$)	6.4 ± 1.6	4.1 ± 1.3	−4.326	**<0.001**
Control group ($n = 33$)	5.4 ± 2.4	6.7 ± 1.6	−4.283	**<0.001**
Z value	−1.643	−5.081		
p-value[b]	0.100	**<0.001**		
Frequency of daily use of lip balm (hamamelis ointment)				
Mesotherapy group ($n = 25$)	4.9 ± 2.1	2.8 ± 1.3	−3.872	**<0.001**
Control group ($n = 33$)	5.4 ± 3.3	5.9 ± 2.7	−4.305	**<0.001**
Z value	−0.730	−4.474		
p-value[b]	0.465	**<0.001**		
Negative impact of existing cheilitis/dryness on your quality of life (VAS, 0–10)				
Mesotherapy group ($n = 25$)	7.8 ± 1.8	5.0 ± 1.8	−3.611	**<0.001**
Control group ($n = 33$)	6.1 ± 2.0	7.1 ± 1.6	−4.221	**<0.001**
Z value	−3.149	−4.043		
p-value[b]	**0.002**	**<0.001**		

Note: Data are expressed as mean ± standard deviation. Significant values were shown in bold.

Abbreviations: ICGS, Isotretinoin Cheilitis Grading Scale; ISO, Isotretinoin; VAS, Visual Analog Scale.

[a]Wilcoxon test was used for comparisons of two dependent samples.

[b]Mann–Whitney *U* test was used for independent samples.

4 | DISCUSSION

Mucocutaneous toxicity, which often occurs with systemic retinoids, is manifested by decreased sebum production and stratum corneum thickness, and altered skin barrier function.[10] Due to the weak barrier function and low water holding capacity, the lips become highly sensitive to environmental factors and some drugs.[11] Patients receiving ISO usually develop cheilitis within days to a few weeks after starting treatment. In routine clinical administration of the drug, cheilitis begins within the first 7 days of therapy and marks

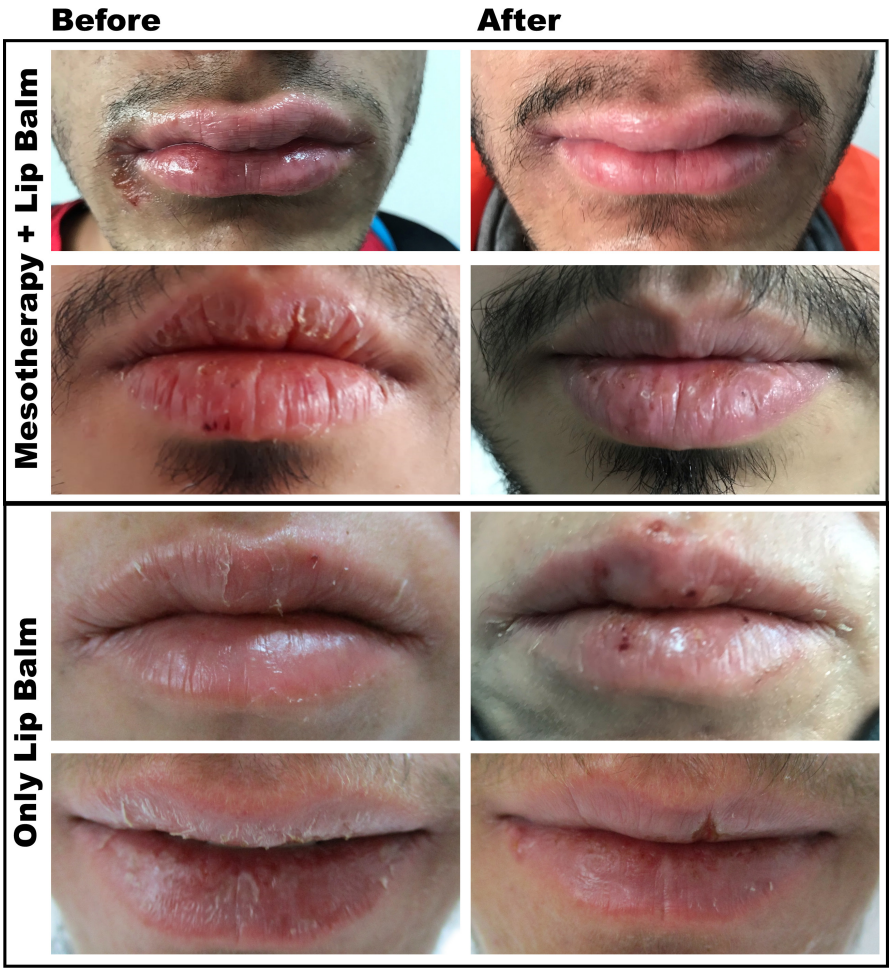

FIGURE 1 One-month follow-up results of patients who received dexpanthenol mesotherapy on the lips and only used lip balm including hamamelis ointment

the onset of the sebo-suppressive effect. Cheilitis is a marker of adequate bioavailability and can be used to individualize the optimal dose of the drug.[2] However, cheilitis causes serious discomfort in patients. Severe cheilitis can affect food intake and speech.[11,12] It also predisposes patients to secondary local bacterial, viral, and fungal infection.[13] These side effects may affect the patient's compliance with treatment. Therefore, it is extremely important to discover effective treatments for this major problem. In the treatment of ISO-induced cheilitis, it is recommended to use petroleum jelly at night and lip balms with SPF sunscreen filters during the day, frequently and abundantly.[11,12,14] Hamamelis ointment can also be used in the treatment and prophylaxis of cheilitis with its anti-inflammatory, keratinocyte proliferation, and differentiation effects.[15,16] All the participants in our study used only hamamelis ointment as a lip balm to the extent of their needs. We found DXP mesotherapy to be more effective than the use of hamamelis ointment, even with a single injection. We found a dramatic improvement in the findings of erythema, squam/crust, fissure, and angular cheilitis in patients who were re-evaluated 1 month after mesotherapy, although 80% of the patients reported that the duration of the effect of mesotherapy was less than 4 weeks. Contrarily, in patients using hamamelis ointment alone, further exacerbation of these findings was observed 1 month later. In many studies, other non-conventional treatments such astrichloroacetic acid (TCA) peeling, topical primrose oil, topical vitamin E, and oral omega-3 supplement have been tried in the treatment of ISO-related cheilitis.[12,17–19] Mansouri et al. reported that 33% TCA had a clinically significant effect on the improvement of oral ISO-related cheilitis findings such as especially erythema and commissure.[12] It was reported that the combination of oral Vitamin E and ISO in the treatment of acne was ineffective on ISO-related cheilitis.[20] To date, there is no proven effective prophylactic treatment protocol for ISO-induced cheilitis.

Dexpanthenol is a medical agent that can be used topically, parenterally, and intradermally. Topical medication of DXP is widely used in clinical practice to accelerate wound healing.[21] However, intradermal DXP is mostly used in combination with various active ingredients for skin rejuvenation and hair loss.[22,23] To the best of our knowledge, there is no study on intradermal DXP medication in the treatment of cheilitis. DXP functions such as a humidifier: increase stratum corneum hydration, reduce trans-epidermal water loss, and maintain skin softness and elasticity. Also, DXP has been shown to stimulate re-epithelialization and granulation and has antipruritic and anti-inflammatory effects on experimental ultraviolet-induced erythema.[6,21] DXP is a safe agent.[6] We did not notice any side effects related to the procedure, except for edema, ecchymosis, and pain, which were not serious and did not last long. The lack of a relationship between the desire to continue mesotherapy with repetitive sessions and the severity of the pain suggested that the procedure-related pain is not the main limiting factor in mesotherapy. Although the high efficacy of the

TABLE 5 Side effects of lip mesotherapy and patient opinions on the treatment

Procedure-associated side effects ($n = 25$)	
Pain (VAS, 0–10)	4.6 ± 1.4; range: 2–8
Duration of lip edema (h)	1.1 ± 0.5; range: 0.5–3
Ecchymosis	1 (4.0%)
Others	0 (0.0%)
The patients' opinions in the mesotherapy group regarding the treatment	
Satisfaction level ($n = 25$)	
Very satisfied	4 (16.0%)
Satisfied	13 (52.0%)
Slightly satisfied	7 (28.0%)
Unsatisfied	1 (4.0%)
The day of improvement after the procedure (day)	3 ± 1.5; range: 1–7
Effect duration ($n = 25$)	
≥4 weeks	5 (20.8%)
2–4 weeks	12 (50.0%)
≤2 weeks	7 (29.2%)
Desire to request the procedure in your follow-up ($n = 25$)	
So willing	1 (4.0%)
Willing	13 (52.0%)
Undecided	5 (20.0%)
Never	6 (24.0%)

Note: Data are expressed as mean ± standard deviation; minimum and maximum or *n* (%).

Abbreviation: VAS, Visual analog scale.

procedure and high satisfaction levels of the patients were noted; one-fourth of the patients stated that they would not consider having the procedure again. This situation stands before us as a challenge in patient selection.

The small sample size is the main limitation of the study. Transepidermal water loss measurement was not included in the protocol due to our technical impossibility.

In conclusion, DXP mesotherapy seems to be a so effective option in the treatment of ISO-related cheilitis. We achieved statistically significant high efficacy rates despite the small number of patients. Therefore, we believe that the combination of DXP mesotherapy with other routinely prescribed emollients may be a good option to increase compliance with ISO treatment. We think that DXP mesotherapy is an easily available, inexpensive, safe, practical, and effective method in the treatment of cheilitis.

CONFLICT OF INTEREST

There is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception and design; N.M, acquisition of data; T.K, analysis and interpretation of data; Ç.T, drafting the manuscript; N.M, T.K, Ç.T revising it critically for important intellectual content; N.M, T.K, Ç.T.

ETHICAL APPROVAL

The study protocol was approved by the ethics committee of the Erzurum Regional Training and Research Hospital (reference no. 2021/12-187).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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