EFFICACY OF THE COMBINATION OF FRACTIONAL LASER CO_2 AND NARROWBAND ULTRAVIOLET B IN THE TREATMENT OF NON-SEGMENTAL VITILIGO

Tran Thi Thu Hien[1], Le Huu Doanh[1,2]

SUMMARY

Objectives: To evaluate the efficacy of the combination of fractional laser CO_2 and narrowband ultraviolet B (NB-UVB) in the treatment of non-segmental vitiligo.

Materials and methods: An prospective half-body comparative clinical study, was conducted on 31 lesions of vitiligo in 17 patients with non-segmental vitiligo. Patients were treated with 3 monthly sessions of half-body fractional laser CO_2 and NB-UVB was administered to the entire body 5 days after each fractional laser interval 3 times per week for 4 months. Objective clinical assessments were evaluated on the area of the lesion using Adobe Lightroom program, adverse effects, and patient satisfaction.

Results: There was a good improvement in the repigmentation on laser side compared to control side, but not significant. The improvement was statistically significant on laser side than control side on trunk and in the group of stable vitiligo. We observed the mix repigmentation of marginal and perifollicular was the most frequent (48,4%). Noticeable adverse effects were pain, burning sensation, erythema, swelling, pruritus and hyperpigmentation. No activated vitiligo, Koebner phenomenon, infection or scarring was found in our patients.

Conclusion: The combination of fractional laser CO_2 and NB-UVB could be considered a safe treatment of stable non-segmental vitiligo, especially on trunk.

Keywords: *Vitiligo, non-segmental vitiligo, laser, NB-UVB.*

1. INTRODUCTION

Vitiligo is an acquired pigmentary disorder of unknown origin. It is characterised by the development of white macules due to a lack of functioning melanocytes in the skin and/or hair. The estimated prevalence is 1% of the population.[1] It affects people of all ages and genders; but usually appears in the second or third decade of life. The exact etiology of vitiligo is still unknown[2]. Several hypotheses were considered such as the autoimmune or autoinflammatory theory, genome-related theory, innate immune response, active oxygen species and therefore melanocyte-intrinsic abnormalities[1]. This disease has an unpredictable course and variable response to treatment. Nowadays, there are several treatment modalities which have been used for treatment such as corticosteroids, immune-modulators, analogues of vitamin D3, phototherapy, laser and surgery[3,4]. Phototherapy is proved to be of

1: Hanoi Medical University
2: National Hospital of Dermatology and Venereology

high efficacy, better tolerated and superior to the other lines of treatment, so it is widely used although it may require more than 1 year for its completion.[5] Some combinations were studied recently with many therapeutic modalities such as erbium:YAG laser, dermabrasion, topical and intradermal 5-fluorouracil…[6-8] and laser CO_2[9-11] with promising results. Given the need to improve the therapeutic response of vitiligo, the purpose of this study is to evaluate the efficacy of the combination of fractional laser CO_2 and narrowband ultraviolet B (NB-UVB) in the treatment of non-segmental vitiligo.

2. SUBJECTS AND METHODS

2.1. Subjects

Patients with non-segmental vitiligo at National Hospital of Dermatology and Venerology from 07/2021 to 09/2022, with the criteria:

Inclusion criteria: Patients were at least 18 years old and diagnosed with non-segmental vitiligo at any sites or periods. Patients were explained and agreed to join this study.

Exclusion criteria: Patients having any one of the following conditions were excluded: acute infection, history of Koebner phenomenon, keloid, hypertrophic scar or photosensitivity, treated with systemic therapy, topical therapy, phototherapy or laser therapy in one recent month, contraindication of phototherapy, pregnant and lactating women, hypersensitivity with any ingredients of any medicines used in this study.

2.2. Research methods

2.2.1. Study design: An prospective half-body comparative clinical study (377-HĐĐĐ-BVDLTW)

2.2.2. Treatment procedure

For each patient, one side of the body (if the patient has bilateral symmetrical lesions) or one side of the lesion (if the patient doesn't have bilateral symmetrical lesions) was treated with NB-UVB alone (control side), while the other side was treated in addition to 3 sessions of monthly fractional CO_2 interval (laser side). The total duration of the treatment was 16 weeks.

For fractional laser CO_2 therapy: the patient was applied local anesthetic cream (Emla cream) with occlusion for 60 minutes before starting the laser. Then we used the fractional laser CO_2 (Ami Bioxel by SJ Global - Korea) for 1 pass, with the energy of 180 - 200mJ, density level 144 dots/cm^2, depth level 1 on laser side of the lesion and 2mm-rim of normal skin. The total area for each patient did not exceed $30cm^2$. After the session of laser, we applied a cold compress and then topical antibiotic cream (Tyrosur gel) for 5 days. Then NB-UVB was applied to both sides 3 times weekly.

For NB-UVB therapy: All patients received 3 sessions of NB-UVB (Medisun Psori-Kamm UVB-311 - Germany) on both sides per week, starting dose was 150 mJ/cm^2, then increased by 50mJ every session till the minimal erythema dose was achieved.

2.2.3. Clinical and follow-up assessment

Photos were taken at baseline, monthly for 4 months at the same distance and the same position. The area of vitiliginous lesions was measured in pixels using Adobe Lightroom program. The percentage change in the area of vitiligo lesion on each side was calculated using the following equation:

$$Percentage\ change = \frac{Area\ before\ treatment - Area\ after\ treatment}{Area\ before\ treatment} x\ 100\%$$

The repigmentation response was evaluated as follows: excellent (grade 4): > 75%, good (grade 3): > 50 - 75%, moderate (grade 2): > 25 - 50%, mild (grade 1): 1 - < 25% and no response (grade 0).

The patients were informed to report any complication occurred: pain, burning sensation, erythema, infection, hyperpigmentation, swelling, pruritus… and their satisfaction.

At the end of the treatment, the patient decided to follow this therapy on control side or not, depending on his/her satisfaction.

2.2.3. Statistical analysis

The data was analysed using Stata software, version 15.0. Qualitative data were described using numbers and percentages. Quantitative data were described using range (minimum and maximum), mean, standard deviation, and medium. Wilcoxon signed-rank test was used to compare between combination treatment and NB-UVB only. The significance of the obtained results was judged when p value ≤ 0.05.

3. RESULTS

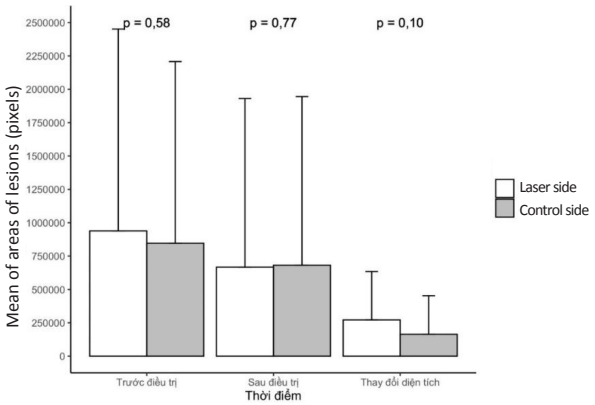
The study included 31 lesions on 17 patients with non-segmental vitiligo. There were 8 males (52.9%) and 9 females (47.1%), the average age was 29.9 ± 10.7, the average duration of disease was 6.1 ± 4.9 months, the average age of onset was 25.8 ± 11.7. 76.47% of patients had vitiligo vulgaris, 58.9% localised vitiligo and 23.53% acrofacial vitiligo. Stable vitiligo was 23.5%, and the others had active vitiligo. The clinical characteristics of the patients involved are summarized in Table 1. 31 studied lesions included 12 on trunk (38.7%), 10 on face and neck (32.3%), 5 on extremities (16.1%) and 5 on acral area (12.9%).

Table 1. Clinical characteristics of the patients involved

			$\underline{x}$ ± SD	Min - Max
Age (year)			29.9 ± 10.7	19 - 51
Age of onset (year)			25.8 ± 11.7	6 - 52
Duration of vitiligo (month)			6.1 ± 4.9	1 - 22
			n	%
Gender	Male		8	52.9
	Female		9	47.1
Type of vitiligo	Acrofacial		2	23.53
	Vulgaris		10	76.47
	Localised		5	58.9
VIDA	Stable	-1	0	0
		0	4	23.5
	Active	1	0	0.0
		2	7	42.2
		3	2	11.8
		4	4	23.5
Used therapy	Topical therapy		14	82.3
	NB-UVB		3	17.6
	Systemic corticosteroid		3	17.6
	None		4	23.5
Total			17	100.0

3.1. Results of the combination of fractional laser CO_2 and NB-UVB in non-segmental vitiligo

The mean changed area of vitiligo lesions was more on laser side than control side but insignificant (p = 0.1) (Figure 3). After treatment, all the lesions improved on laser side with 38.7% mild improvement, 25.8% moderate improvement, 25.8% good improvement and 9.7% excellent improvement. Compared with control side, there were 12.9% of lesions didn't improve, 41.9% showed mild improvement, 16.1% showed moderate improvement, 16.1% showed good improvement and 12.9% showed excellent improvement. But there was no statistical difference between the 2 sides (Table 2). The most frequent type of repigmentation was the mix repigmentation of marginal and perifollicular (48.4%).



P - Wilcoxon signed rank test

Figure 1. Area of the lesions before and after treatment

With regard to the body site, vitiligo lesions on trunk showed a significantly better response on laser side than control side (p = 0.04), while other sites didn't show any significant difference (Figure 2). With regard to the stability of the disease, we noted that there was a significant response in stable vitiligo (p = 0.01) (Table 3).

Table 2. Repigmentation before and after treatment

Side / Repigmentation (%)	Laser side n = 31		Control side n = 31		p
	n	%	n	%	
None (< 0%)	0	0	4	12.9	
Mild (1 - 24%)	12	38.7	13	41.9	
Moderate (25 - 50%)	8	25.8	5	16.1	
Good (51 - 75%)	8	25.8	5	16.1	
Excellent (> 75%)	3	9.7	4	12.9	
Overall ($\underline{x}$± SD)	40.4 ± 30.3		24.9 ± 29.6		0.07
Mean repigmentation score ($\underline{x}$± SD)	2.06 ± 1.03		1.74 ± 1.26		0.098

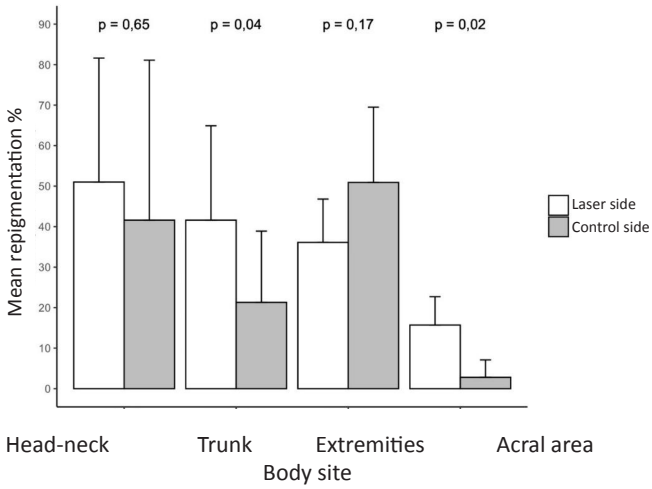


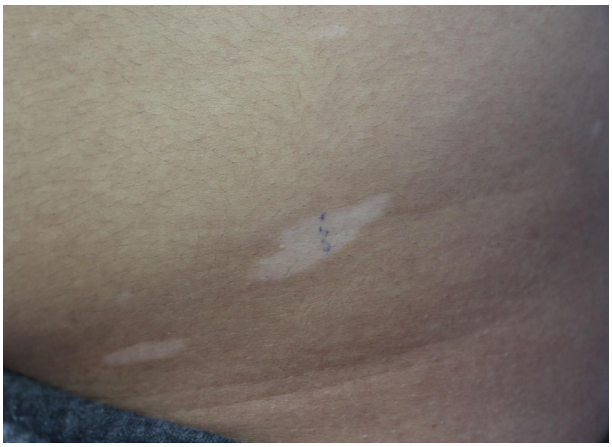
Figure 2. Mean repigmentation in different body parts

Side Repigmentation (%)	Laser side n = 31	Control side n = 31	p
	$\underline{x}$ ± SD	$\underline{x}$ ± SD	
Stable	34.3 ± 21.5	13.1 ± 13.6	0.01
Active	43.3 ± 26.5	38.4 ± 31.8	0.50

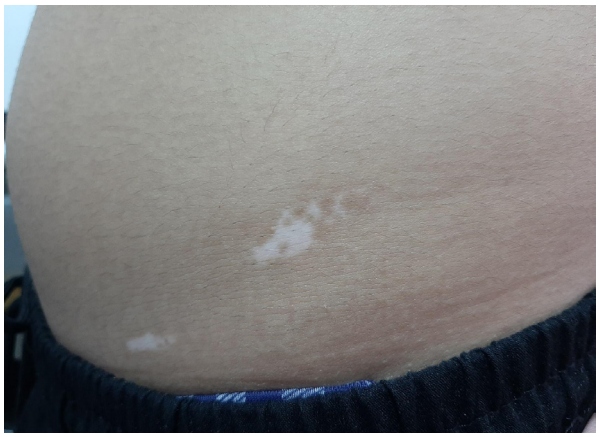
Table 3. Mean repigmentation and the stability of vitiligo

3.2. Safety assessment of the combination of fractional laser CO_2 and NB-UVB in non-segmental vitiligo

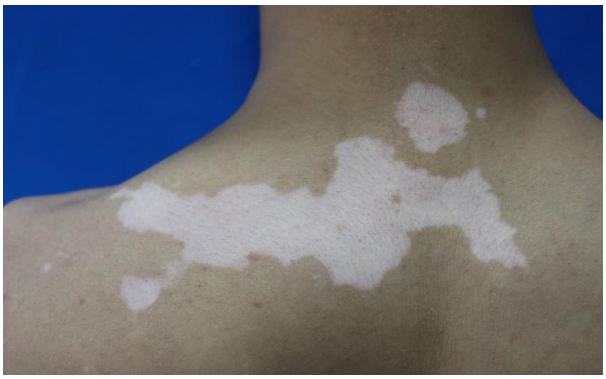
In our study, our patients experienced pain (82.4%), burning sensation (70.6%), erythema (58.8%), mild swelling (11.8%) and pruritus (23.5%) after laser session. However, these symptoms were relieved within 1 - 2 days, and were accepted by all patients. There were 3 patients experiencing hyperpigmentation, no patients with Koebner phenomenon, activated vitiligo, scarring or infection. 41% of patients were satisfied and 35% of patients were very satisfied with the therapy.



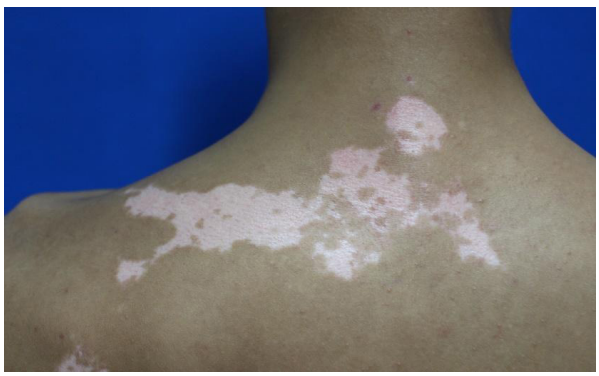
Before treatment



After treatment



Before treatment



After treatment

Figure 3. The improvement after treatment. A - control side, B- laser side

4. DISCUSSION

In our study, we analysed the efficacy of fractional CO_2 laser combined with NB-UVB, compared with NB-UVB alone in the treatment of non-segmental vitiligo. All the lesions improved on laser side with 38.7% mild improvement, 25.8% moderate improvement, 25.8% good improvement and 9.7% excellent improvement. By comparing the improvement between 2 sides, there was no significance ($p > 0,05$). This result is shared by Mohamed Bakr El-Zawahry (2017)[10] who also used the area of vitiliginous lesions on the graphics program and noted that the improvement was -11.4% on laser side, better than on control side -9.4%, but insignificant. According to Pelin Eşme (2019)[12], the mean repigmentation score was insignificantly lower on laser side (0.35 ± 1.09) than control side (0.82 ± 0.16). However, certain studies show better results when combining these therapies. Doghaim (2018)[7] found that about 69% of the patients treated with the combination of fractional laser CO_2 and NB-UVB showed minimal to excellent improvement, while 18.7% of the patients treated with NB-UVB alone showed minimal to good improvement. By comparing the degree of improvement between both groups, the author found the difference was statistically significant ($p = 0.007$). J.Shin (2011)[9], studied on refractory non-segmental vitiligo, and found the mean improvement scores assessed by physicians were significantly higher for those treated with half-body fractional CO_2 laser therapy followed by NB- UVB phototherapy, compared with those treated with NB-UVB alone ($p = 0.034$).

The differences between these studies can be explained by the different treatment procedures, sample sizes, patients… Although, we all shared opinions about the mechanism of laser CO_2 on vitiligo. It is well established that CO_2 resurfacing laser produces immediate tissue retraction and this shrinkage can be explained by the denaturizing of collagen bundles[13]. This shrinkage over treated skin surface may contribute to the narrowing of the vitiligo lesions. In addition, melanogenic cytokines were released during the inflammation and wound healing process[8]. This includes the release of matrix metalloproteinase-2 which stimulated melanocyte stem cells migration from adjacent normal skin, hair bulb, and outer root sheath[14]. The exact mechanism is still unknown, so further studies need to be done to find the answer.

We also found that there was a significant difference in the response of different body parts. The trunk showed significantly better response on laser side than on control side, while other parts (head and neck, extremities, acral site) didn't show any difference. The acral part is confirmed to be difficult to repigment because of thick skin and low hair follicle density, which is the reservoir of melanocytes[15]. The head and neck often show good result to phototherapy and topical steroids, so the laser treatment doesn't offer any additional benefit compared to other conventional treatments[16].

Moreover, stable vitiligo showed better repigmentation on laser side than on control side, which was not found in active vitiligo. The explanation for this phenomenon, in our opinion, is the excessive change of the inflammatory-related factors in active vitiligo treated with laser CO_2, which can bring negative effects to the repigmentation process. Some evidences were found on the literature: In the study of Lin M[17], active vitiligo lesions showed lower transforming growth factor β1 (TGF-β1) than stable vitiligo

and control groups which suggested that TGF-β1 played an important role in vitiligo. In another study of Makboul M[18], the effect of fractional CO_2 laser on patients with hypertrophic scars showed that TGF-β1 expression was significantly decreased in skin samples taken 6 months after application of fractional CO_2 laser on hypertrophic scar than in the samples taken before treatment. Therefore, laser CO_2 can contribute to the instability of active vitiligo, then prevent the lesion from repigmentation.

In our study, our patients experienced pain (82.4%), burning sensation (70.6%), erythema (58.8%), mild swelling (11.8%) and pruritus (23.5%) after laser session. However, these symptoms were relieved within 1 - 2 days, and were accepted by all patients. There were 3 patients experiencing hyperpigmentation, no patients with Koebner phenomenon, activated vitiligo, scarring or infection. This combination can be since considered a safe therapy.

The limitation of our study is the small sample size and short follow-up period, which would enable us to evaluate exactly the difference between 2 sides, the longevity of the repigmentation and also to distinguish from post-inflammatory hyperpigmentation on histopathologic sample.

5. CONCLUSION

In conclusion, our study demonstrated that the combination of fractional laser CO_2 and narrowband ultraviolet B (NB-UVB) can be considered a safe therapy, in the treatment of stable non-segmental vitiligo, especially on trunk.

REFERENCES

1. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. *Lancet Lond Engl*. 2015;386(9988):74-84. doi:10.1016/S0140-6736(14)60763-7.
2. Alikhan A, Felsten LM, Daly M, Petronic-Rosic V. Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. *J Am Acad Dermatol*. 2011;65(3):473-491. doi:10.1016/j.jaad.2010.11.061.
3. Mohammad TF, Al-Jamal M, Hamzavi IH, et al. The Vitiligo Working Group recommendations for narrowband ultraviolet B light phototherapy treatment of vitiligo. *J Am Acad Dermatol*. 2017;76(5):879-888. doi:10.1016/j.jaad.2016.12.041.
4. Daniel BS, Wittal R. Vitiligo treatment update. *Australas J Dermatol*. 2015;56(2):85-92. doi:10.1111/ajd.12256.
5. Nicolaidou E, Antoniou C, Stratigos AJ, Stefanaki C, Katsambas AD. Efficacy, predictors of response, and long-term follow-up in patients with vitiligo treated with narrowband UVB phototherapy. *J Am Acad Dermatol*. 2007;56(2):274-278. doi:10.1016/j.jaad.2006.09.004.
6. Abdelwahab M, Salah M, Samy N, Rabie A, Farrag AR. Effect of Topical 5-Fluorouracil Alone versus Its Combination with Erbium:YAG (2940 nm) Laser in Treatment of Vitiligo. *Clin Cosmet Investig Dermatol*. 2020;Volume 13:77-85. doi:10.2147/CCID.S225881.

7. Doghaim NN, El-Tatawy RA, Ismail MA, Ali DAM, El Attar YA. Study the effect of erbium:YAG laser plus topical 5-flurouracil in stable vitiligo resistant to NB-UVB phototherapy. *J Cosmet Dermatol*. 2020;19(1):122-130. doi:10.1111/jocd.13134.
8. Gauthier Y, Anbar T, Lepreux S, Cario-André M, Benzekri L. Possible Mechanisms by Which Topical 5-Fluorouracil and Dermabrasion Could Induce Pigment Spread in Vitiligo Skin: An Experimental Study. *ISRN Dermatol*. 2013;2013:1-7. doi:10.1155/2013/852497.
9. Shin J, Lee JS, Hann SK, Oh SH. Combination treatment by 10 600 nm ablative fractional carbon dioxide laser and narrowband ultraviolet B in refractory nonsegmental vitiligo: a prospective, randomized half-body comparative study. *Br J Dermatol*. 2012;166(3):658-661. doi:10.1111/j.1365-2133.2011.10723.x
10. El-Zawahry MB, Zaki NS, Wissa MY, Saleh MA. Effect of combination of fractional CO2 laser and narrow-band ultraviolet B versus narrow-band ultraviolet B in the treatment of non-segmental vitiligo. *Lasers Med Sci*. 2017;32(9):1953-1958. doi:10.1007/s10103-017-2290-y.
11. Ghasemloo S, Gauthier Y, Ghalamkarpour F. Evaluation of using fractional CO2 laser plus NB-UVB versus NB-UVB alone in inducing marginal repigmentation of vitiligo lesions. *J Dermatol Treat*. 2019;30(7):697-700. doi:10.1080/09546634.2018.1564232.
12. Eşme P, Gür Aksoy G, Elçin G. No Additional Benefit of Combining Fractional Carbon Dioxide Laser With Narrow-Band Ultraviolet B Phototherapy for Vitiligo: A Randomized Prospective Study With Half-Body Side Comparison. *Dermatol Surg Off Publ Am Soc Dermatol Surg Al*. 2019;45(12):1627-1634. doi:10.1097/DSS.0000000000001890.
13. Holme SA, Beattie PE, Fleming CJ. Cosmetic camouflage advice improves quality of life. *Br J Dermatol*. 2002;147(5):946-949. doi:10.1046/j.1365-2133.2002.04900.x
14. Kumar R, Parsad D, Kanwar AJ, Kaul D. Altered levels of Ets-1 transcription factor and matrix metalloproteinases in melanocytes from patients with vitiligo. *Br J Dermatol*. 2011;165(2):285-291. doi:10.1111/j.1365-2133.2011.10324.x
15. Chen GY, Hsu MML, Tai HK, et al. Narrow-Band UVB Treatment of Vitiligo in Chinese. *J Dermatol*. 2005;32(10):793-800. doi:10.1111/j.1346-8138.2005.tb00847.x
16. Kanokrungsee S, Chanprapaph K, Chaiyabutr C, Vachiramon V. A comparative study of combined treatment with fractional carbon dioxide and targeted ultraviolet B phototherapy for facial vitiligo. *Lasers Med Sci*. 2016;31(7):1343-1349. doi:10.1007/s10103-016-1982-z.
17. Lin M, Zhang BX, Shen N, et al. Regulatory T cells from active non-segmental vitiligo exhibit lower suppressive ability on CD8+CLA+ T cells. *Eur J Dermatol*. 2014;24(6):676-682. doi:10.1684/ejd.2014.2436.
18. Makboul M, Makboul R, Abdelhafez AH, Hassan SS, Youssif SM. Evaluation of the effect of fractional CO2 laser on histopathological picture and TGF- β 1 expression in hypertrophic scar. *J Cosmet Dermatol*. 2014;13(3):169-179. doi:10.1111/jocd.12099.