Chulalongkorn Medical Journal

Volume 61
Issue 3 *May 2017*

Article 2

5-1-2017

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Chula Med J Vol. 61 No. 3 May - June 2017

Randomized placebo-controlled trial comparing efficacy of nonablative fractional photothermolysis combined with topical calcipotriol for the treatment of keloid and hypertrophic scar

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Pongprutthipan M, Rojarayanont N. Randomized placebo-controlled trial comparing efficacy of nonablative fractional photothermolysis combined with topical calcipotriol for the treatment of keloid and hypertrophic scar. Chula Med J 2017 May – Jun;61(3): 293 - 305

Background : *Nonablative fractional laser resurfacing has been shown to have size reduction effect on hypertrophic scar with minimal side effects; and antifibrotic effect of vitamin D in keloid fibroblasts has been reported in vitro. A combination of the two treatments should gain additional benefits from facilitation of wound healing, transdermal drug delivery and recurrence prevention.*

Objectives : *To evaluate the efficacy of nonablative fractional laser resurfacing combined with topical calcipotriol for the treatment of keloid and hypertrophic scar.*

Methods : *Subjects were treated with six fractional 1,550 nm Ytterbium/Erbium: fiber laser treatment weekly for entire lesion. Each lesion was randomly treated with topical calcipotriol or white petrolatum twice daily. Follow-up visits were done at week 6th and 12th. Clinical appraisal achieved by Patient and Observer Scar Assessment Scale (POSAS) and evaluator blinded photographic clinical assessment.*

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Results : *Twelve subjects completed treatments in the study. Mean POSAS showed significant reduction (P <0.05) at week 6 but no statistical difference between groups was observed. Photographic clinical assessment had mild (1 - 25%) to moderate (26 - 50%) improvement in majority of the cases but there was no statistical difference between groups.*

Conclusion : *Nonablative fractional laser is an effective treatment for keloids and hypertrophic scars while the benefit of topical calcipotriol could not be demonstrated in the study.*

Keywords : *Fractional erbium laser, hypertrophic scar, keloid, vitamin D_3 analogue, topical calcipotriol.*

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Received for publication. February 27, 2017.

มาริษา พงศ์พฤฒิพันธ์, ณัฐพร โรจน์อารยานนท์. การศึกษาแบบสุ่มเพื่อเปรียบเทียบประสิทธิภาพของเลเซอร์ลอกผิว 1550 นาโนเมตรชนิดแบ่งส่วนร่วมกับยาทาคาลซิโพไทรออลเทียบกับยาหลอกในการรักษาคีลอยด์ และแผลเป็นนูน. จุฬาลงกรณ์เวชสาร 2560 พ.ค. – มิ.ย.;61(3): 293 – 305

เหตุผลของการทำวิจัย : *การรายงานรักษาด้วยเลเซอร์แบบแบ่งส่วนสามารถลดขนาดรอยแผลเป็นชนิดนูน (hypertrophic scar) โดยมีผลข้างเคียงน้อย นอกจากนี้ยังมีการศึกษาผลของวิตามินดีที่มีผลต้านการเกิดพังพืด (antifibrotic effect) ในหลอดทดลอง*

วัตถุประสงค์ : *เพื่อศึกษาประสิทธิภาพและความปลอดภัยของการรักษาคีลอยด์และแผลเป็นนูนด้วยเลเซอร์ลอกผิวระบบแบ่งส่วนร่วมกับการทายาคาลซิโพไทรออล (อนุพันธ์ของวิตามินดี) เปรียบเทียบการรักษาด้วยเลเซอร์ลอกผิวระบบแบ่งส่วนร่วมกับทายาหลอก*

วิธีการศึกษา : *อาสาสมัครผู้มีคีลอยด์หรือแผลเป็นนูนได้รับการรักษาด้วยเลเซอร์ลอกผิวระบบแบ่งส่วน Fractional 1,550 nm Ytterbium/Erbium: fiber laser ทั่วบริเวณแผลเป็น ทุก 1 สัปดาห์รวม 6 ครั้ง ร่วมกับสุ่มให้รอยโรค 2 รอยให้ทายาคาลซิโพไทรออลหรือยาหลอก โดยให้ทาวันละ 2 ครั้ง ติดตามอาการสัปดาห์ที่ 6 และ 12 ประเมินผลการรักษาด้วยแบบประเมิน Patient and Observer Scar Assessment Scale (POSAS) และประเมินการเปลี่ยนแปลงของรอยโรคจากภาพถ่ายโดยแพทย์ผิวหนัง 2 ท่านโดยใช้ quartile grading scale*

ผลการศึกษา : *อาสาสมัคร 12 ราย ได้รับการรักษาด้วยเลเซอร์ครบ 6 ครั้งและใช้ยาอย่างต่อเนื่องผลค่าเฉลี่ยของ POSAS แสดงให้เห็นว่ามีคะแนนของแผลเป็นลดลงอย่างมีนัยสำคัญ ($P < 0.05$) ในสัปดาห์ที่ 6 แต่ไม่แตกต่างกันทางสถิติระหว่างได้รับยาหลอกและยาทาคาลซิโพไทรออล ผลประเมินการเปลี่ยนแปลงของรอยโรคจากภาพถ่ายโดยไม่ระบุการรักษา พบว่าส่วนใหญ่ลักษณะของแผลเป็นดีขึ้น (ร้อยละ 1 - 25) ถึงปานกลางปรับปรุง (ร้อยละ 26 - 50) แต่ไม่แตกต่างกันทางสถิติระหว่างกลุ่ม*

สรุป : *ประสิทธิภาพของเลเซอร์ลอกผิว 1,550 นาโนเมตรชนิดแบ่งส่วนในการรักษารอยแผลเป็นนูนชนิด hypertrophic และ keloid อยู่ในระดับน้อยถึงปานกลาง ในขณะที่ประโยชน์ของยาทาคาลซิโพไทรออล Calcipotriol ไม่สามารถที่จะแสดงให้เห็นในการศึกษา*

คำสำคัญ : *คีลอยด์, แผลเป็นนูน,เลเซอร์ระบบแบ่งส่วน, วิตามินดี อนาล็อก, ยาทาคาลซิโพไทรออล.*

Keloids and hypertrophic scars are common problems in dermatologic practices. The conventional treatments include intralesional steroid injection which are considered standard treatments. However, the duration of treatment, pain from injection and unpredictable results limit the usage and outcome of the treatment. The current topical treatments for keloids and hypertrophic scars have shown minimal efficacy and are not considered standard treatment.[1, 2] The benefit of vitamin D has been recently reported *in vitro* by Zhang GY, *et al*.[3], that showed the antifibrotic effect of 1,25 vitamin D in keloid fibroblast culture. The effect of serum vitamin D level associated with TaqI gene polymorphisms of vitamin D receptor (VDR) on keloid formation has been shown by Yu D, *et al.* [4] in Chinese patients.

Various laser modalities have been investigated. Fractional 1,550-nm erbium-doped fiber laser resurfacing has been reported to have beneficial results for the treatment of keloids and hypertrophic scar ranging from minimal to moderately improvement with minimal side effects. [5 - 7] Although the precise mechanism of fractional erbium fiber laser in hypertrophic scar skin is currently unknown, it is possible that the columns of thermal injury characterized by localized epidermal necrosis and collagen denaturation initiate a cascade of wound healing that leads to normalization of the collagen synthesis and collagenolysis.[8, 9] The fractional 1,550-nmerbium-doped fiber laser also serves as a drug delivery method.[10] This study is aimed to investigate the efficacy and safety of the combined treatments of topical vitamin D_3 and fractional 1,550-nm erbium-doped fiber laser for the treatment of keloids and hypertrophic scars.

Methods

Patients who had two hypertrophic scars or keloids or one with more than 3 cm in length, age between 18 - 45 years old and who did not receive of any treatment for at least 3 months prior to the study were eligible for the study. Exclusion criteria include chronic liver diseases, renal insufficiency, hypercalcemia and hyperparathyroidism, currently on vitamin D supplement or isotretinoin, history of allergic to eutectic mixture of lidocaine and prilocaine (EMLA®) cream and topical calcipotriol, history of photo aggravated skin diseases, pregnancy and lactation. Two lesions or half of the lesion were randomized (by block of 4) to receive either placebo (vaseline ointment, King Chulalongkorn Memorial Hospital pharmacy preparation) or topical calcipotriol ointment (Daivonex™ ointment, Leo-Pharma, Denmark) which are concealed in similar packages. The topical treatments have been assigned to applied twice daily in conjunction with six treatments of fractional 1,550-nm erbium-doped fiber laser (FINESCAN 1550™, TNC SPECTRONICS, Bangkok, Thailand) every 1 week. Anesthetic cream assigned prior to laser treatment was EMLA™ cream (Astra Zeneca, Wilmington, DE, USA) under occlusion for 60 minutes. The parameter setting for fractional 1,550-nm erbium-doped fiber are 35 - 40 mJ, density 100 dots/cm^2x 4 passes, cumulative density 400 dots/cm^2 with spot size 1 or 2 cm^2. Digital photographs were taken at baseline, 6 weeks and 12 weeks. Clinical appraisal was achieved by Patient and Observer Scar Assessment Scale (POSAS) in English and evaluated by blinded photographic clinical assessment using quartile grading scale. All patients were asked whether they have any difficulty in answering all the English

questionnaires in POSAS. Three dermatologists who were blinded to the treatment were assigned to perform photographic clinical assessment (evaluation of color, texture, size and overall improvement) using quartile grading scale; -4(-76 - 100%),-3(-51 - 75%),-2(-26 - 50%), -1(-1-25%), 0(unchanged),1(1 - 25%), 2(26 - 50%), 3(51 - 75%), 4(76 - 100%). Approval of the ethics committee of the Chulalongkorn University was obtained and all the participants gave their written informed consents. Measured values were expressed as means ± standard deviations. Paired *t*-test and Wilcoxon signed-rank test were performed with SPSS statistical software (version 22.0 IBM, Chicago, IL, USA) to compare the treatment responses between the two groups. *P*-value < 0.05 was considered significant.

Results

Twelve subjects completed all six treatments and 12 weeks of follow up, only one case missed week-6 follow-up visit (Table 1). Intention-to-treat analysis and last observation carried forward was done with nonparametric two related samples statistical analysis, Wilcoxon signed-rank test.

Clinical appraisal was done by Patient and Observer Scar Assessment Scale (POSAS) which composed of the evaluation of pain, pruritus, color, stiffness, thickness, irregularity and overall opinion of the scar rating from 1 (no, normal) to 10(yes, very different by patient rating (Patient Scar Assessment Scale) and the evaluation of vascularity, pigmentation, thickness, relief, pliability and overall appearance of the scar comparing with normal skin rating from 1(normal skin) to 10(worst scar imaginable) by dermatologist (Observer Scar Assessment Scale) were recorded at baseline, week 6^{th} and 12^{th}. (Figure 1) All patients had no difficulty answering any questions in English language. Mean POSAS score showed no difference between the placebo and calcipotriol group (P >0.05). Reduction of scores in both groups showed significantly changes from baseline (P <0.05) at week 6 but there was no statistical significant at 12 weeks.

Evaluator blinded photographic clinical assessment (evaluation of color, texture, size and overall scar improvement) using quartile grading scale, the result at week 6^{th} and 12^{th} are showed in Figure 2 and 3. The results have no statistically significant (P >0.05) between placebo and calcipotriol in all aspects. Digital photos are shown in the Figure 4.

Table 1. Patient characteristics. (n =12)

Age (years) (min – max)	**Mean 35.3 ± 9.3 (21.0 – 57.0 years)**
Female: Male n (%)	9 (75%): 3 (25%)
Keloid: hypertrophic scar n (%)	8 (66.7%): 4 (33.3%)
Skin phototype n (%)	Type III 8 (66.7%), type IV 4 (33.3%)

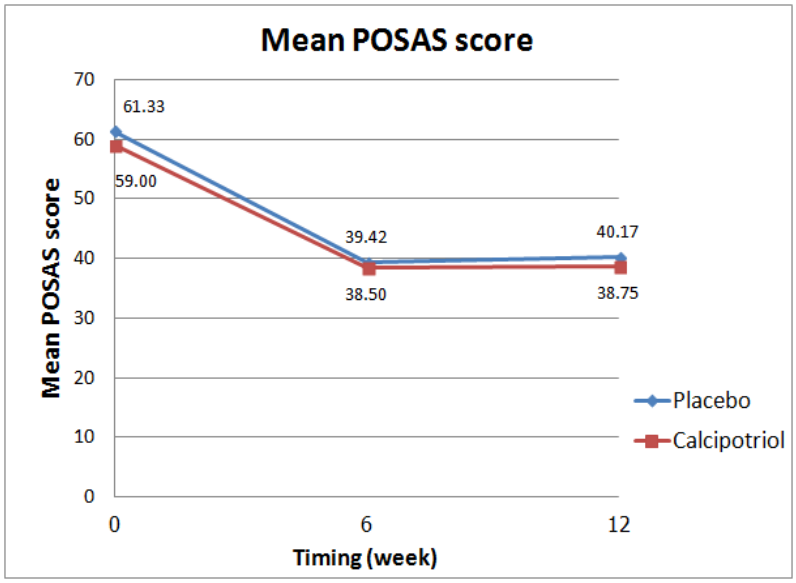

Figure 1. Mean Patient and Observer Scar Assessment Scale (POSAS) at baseline, 6 weeks and 12 weeks. (* P <0.05)

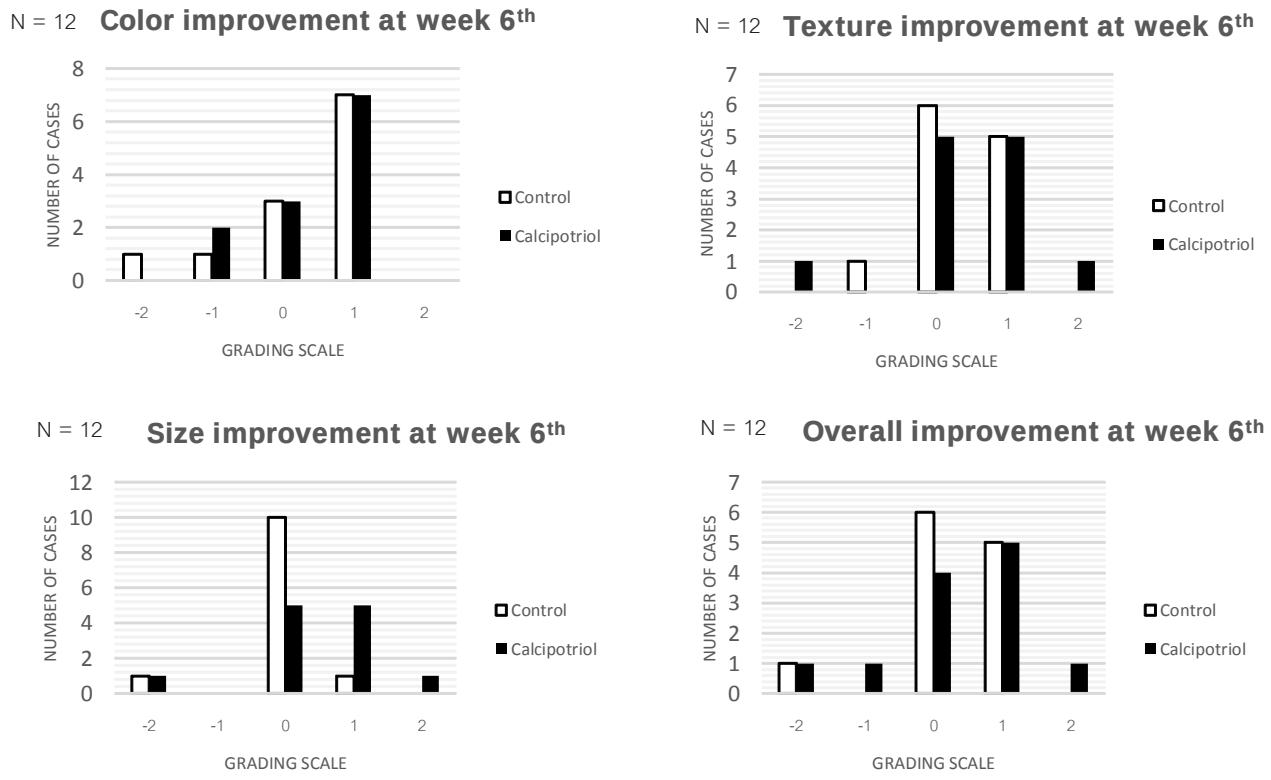

Figure 2. Evaluator blinded photographic clinical assessment at week 6th (n = 12).

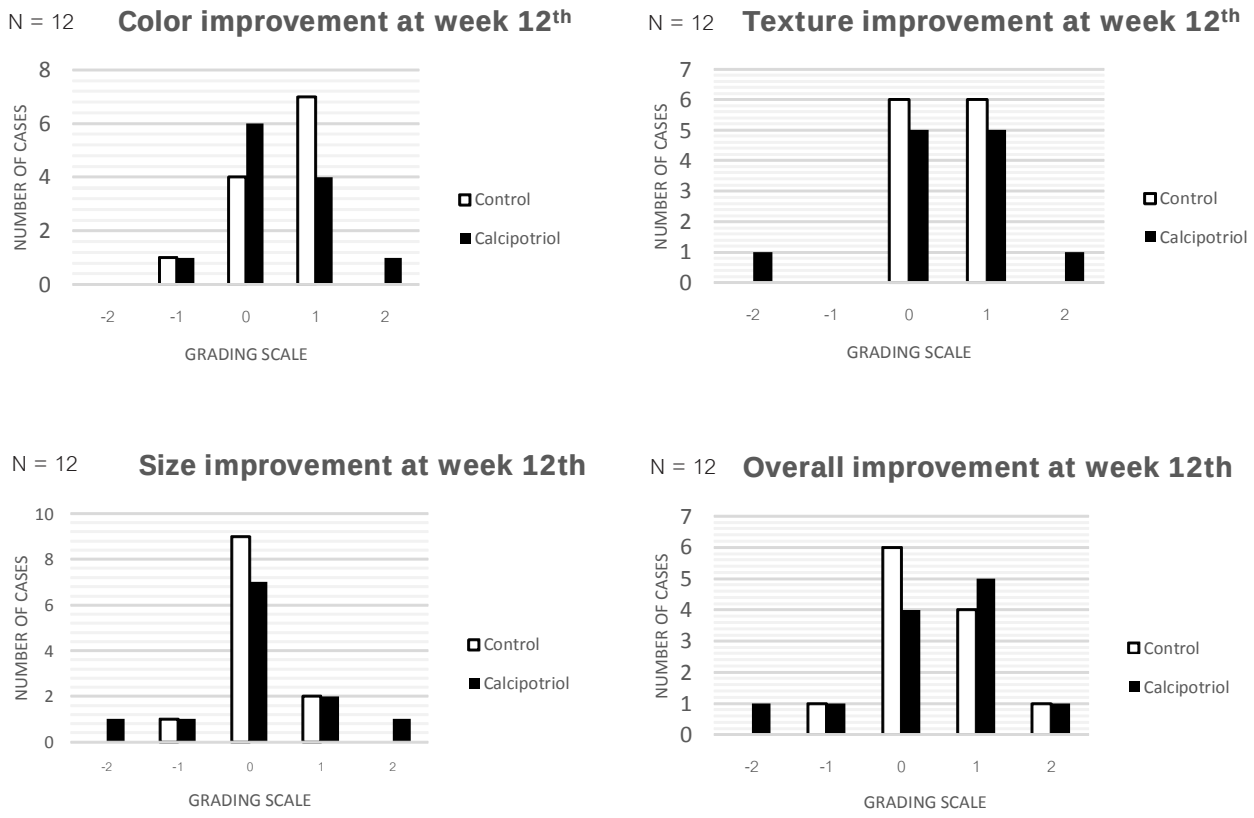

Figure 3. Evaluator blinded photographic clinical assessment at week 12th (n = 12).

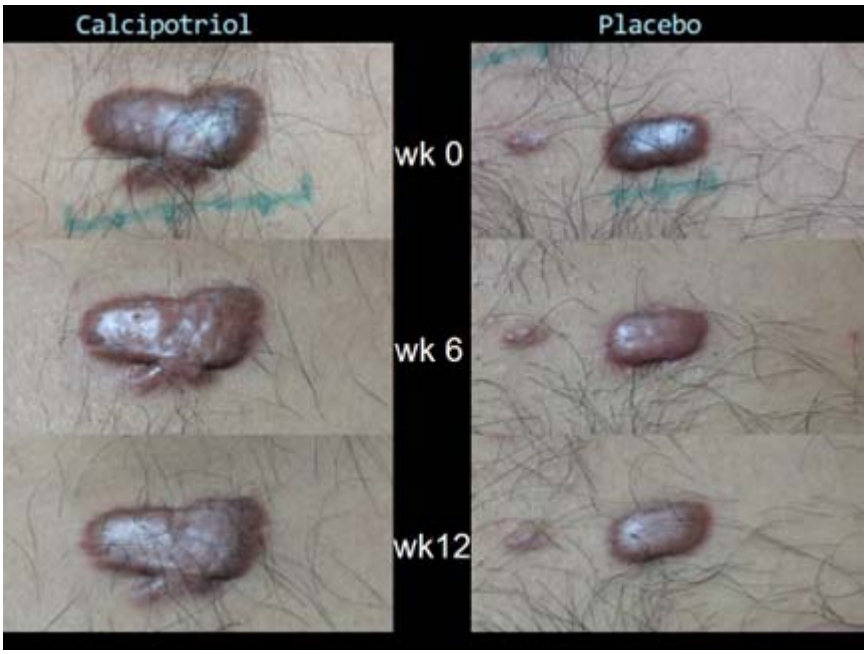

Figure 4. Compared photographic change between baseline, week 6th and week 12th.

Adverse events from fractional 1,550-nmerbium-doped fiber laser include bronzing of the skin, erythema, dryness, burning sensation, itch which lasts for average 4 days. Pain reported by numeric pain rating scale (pain NRS, ranging from 0 - 10) was 1.6 in average (range from 0 - 7).

Calcipotriol side effects has been reported in three patients which are local irritation after the first treatment visit and responded well with topical steroid. All of the adverse events are mild and well-tolerated.

Discussion

Keloid and hypertrophic scar are sequel of the imbalance between collagen synthesis (which under the mechanism of cytokine-mediated fibroblast stimulation especially by transforming growth factor (TGF) – ß and degradation (by matrix metalloproteinase (MMP) enzyme especially by collagenase) during wound healing process. The impact of keloid is statistically significant on the quality of life, self-esteem and social functioning.[11, 12] The treatment has been investigated in many studies. No effective treatment for keloids exists as a definitive cure. The intralesional corticosteroids are standard treatment but the injection pain prevent the patient to receive the continuous treatment and stiffness of the scar is limited the volume of steroids to deliver adequately to the skin. New treatment option that compensate those limitations are explored especially the newer drug delivery method. Furthermore, the limitation of the corticosteroids dosage is also needed to be considered, the amount of intralesional steroids applied in one session may have potentiality to have immunosuppression [13, 14] and also the adverse event if applied in appropriately in the superficial plane of the skin i.e. skin atrophy and telangiectasia. So the requisite of other medication that could replace the corticosteroids usage is under the investigation.

Pathogenesis of keloid is still not well established. The pathogenesis that leads to develop excess collagensis, extracellular matrix production and thickened scar is mediated by main cytokines, especially TGF – ß [15, 16], and decreased matrix metalloproteinase (MMP) enzyme-1, 2, 8 and 9 [17-19] released from malfunctioning fibroblasts.

Vitamin D and its metabolites play important roles in the skin physiology especially on the proliferation and differentiation. Study of vitamin D and keloid fibroblast has been first reported by Zhang GY, *et al*.[3] which demonstrated higher number of vitamin D receptor (VDR) expression in keloid fibroblast than in the normal tissue especially when incubation with 1,25 dihydroxy vitamin D_3. This study also demonstrates the inhibitory effect on the proliferation of keloid fibroblast, suppression of extracellular matrix production, induction of MMP-9 and hepatocyte growth factor (antifibrotic cytokine) in fibroblast culture model. This study has found the potential of vitamin D to be a novel therapy for keloid. The follow in vitro study by Li Y, *et al*. [20] and Halder S, *et al*.[21] and some animal studies [22 - 24] have similar result which illustrated antifibrotic effect of vitamin D. Calcipotriol ointment used in the study is a vitamin D analog which widely used for the treatment of psoriasis vulgaris. The effect includes antiproliferative effect to keratinocytes [25] but the antifibrotic effect in patient with scar has limit study. The only study in human aimed to prevent hypertrophic scar formation which found no statistically significance from placebo.[26]

Niwa AB, *et al*. reported the efficacy of fractional Erbium 1,550 nm fiber laser in hypertrophic scars, 2 - 3 treatments, monthly session with parameter are 35 - 50J/cm^2,treatment level of 6 to 8 (20 -26% of treated area), 8 - 10 passes with total energies of 0.50 - 1.80 kJ delivered per session. The mean improvement grading is 2.4 (from 1 - 4, rating by quartile grading scale).[5] Waibel J, *et al.* demonstrate 60% of the subjects have moderate to excellent overall improvement in burn scars (10 patients, using a quartile scale: 0: none, 1: mild (1 – 33%), 2 :moderate (34 – 66%), 3:excellent (67 – 100%) which consisted of hypo-, hyperpigmentation and atrophic and hypertrophic scars using 1,550 nm nonablative fractional laser (Fraxel ReStore, Solta, Hayward, CA). The energy level ranged from 40 to 70 mJ/pulse with treatment density range from 6 to 13 (17 – 38% tissue coverage). [27] The in vitro studies has shown the effect of fractional erbium laser on MMP regulations and interleukin expression that could play a role for dermal remodeling, anti-inflammatory effects and increased epidermal differentiation. Amann P, *et al.* demonstrate the increase in MMP-7, MMP-9 and MMP-11 in the laser treatment group in 3D skin model [8] which MMP-9 is known enzyme responsible for hypertrophic scar regression in previous study by Reno F, *et al.*[28]

The combination of topical calcipotriol (vitamin D_3 analog) and fractional laser resurfacing may gain additional benefits from facilitation of wound healing [8, 9], transdermal drug delivery [29] and prevent the recurrence [3, 19] from antifibrotic effect of vitamin D.

Our results demonstrate the effect of the fractional 1,550-nmerbium-doped fiber laser in both placebo and calcipotriol treatment group which have significantly reduced one-third of mean POSAS score and also have mild (1 - 25%) to moderate (26 - 50%) improvement in majority of the patient by evaluator blinded digital photography evaluation quartile rating scale but failed to demonstrate the benefit of calcipotriol treatment over placebo. The similar results in the study of calcipotriol alone in the prevention of hypertrophic scar has been showed in the previous study by Van de veer WM, *et al.* which showed no significant difference in the prevalence of hypertrophic scar from mammoplasty scar in the randomized control trial and histologic analysis.[26] Calcipotriol is a synthetic analog of 1 alpha, 25-dihydroxyvitamin D_3, is used in the treatment of psoriasis, binds the intracellular vitamin D receptor for inhibiting human skin cell proliferation. The anti-proliferative effect was accompanied by a change in the cytokeratin pattern of the skin cells, indicating a differentiation-inducing effect.[30, 31] But the study effect of calcipotriol on fibroblast *in vivo* has never been known or reported. Drug penetration and drug level at the dermis may be the contributing factors for the unfavorable outcomes. The previous studies suggest the possible effect of vitamin D and keloids may be mediated through the vitamin D level in the circulation rather than the local vitamin D application. The study in Chinese patients [4] has shown the effect of vitamin D receptor genotype which the odds of having keloids in patients possessing Taq1 CC genotype compared with TC genotype (odds ratio 1.280, P = 0.051). And the investigator is also reported a statistically significant decrease in serum 1,25 hydroxy vitamin D3 in keloid patients compared with control. As well as in the animal study by Sahbaz A, *et al*. has shown the effect of vitamin D supplement that has statistically

difference in the reduction of peritoneal adhesion. The future study should explore the potential of vitamin D supplementation in keloid prevention rather than the topical treatment.

At week 6, there is only one cases that got worse in size and 2 more cases showed worse in overall improvement scores due to keloid progression after complete treatment and those two cases get worse in week 12 as well. These is considered as one of the important adverse events from unstable keloid condition that may progress after any traumatic event from laser treatment. This showed raise an awareness of fractional laser even nonablative type in the unstable keloid.

Other adverse events are minimal and tolerable. The most common is pigmentary change (bronzing), followed by erythema, dryness, itching and burning sensation which last long for short periods of time. Pain is tolerable (1.6 from 10 by pain NRS). Calcipotriol irritation is noted in the first application but no report in the following treatment.

The limitation of this study is unable to demonstrate the different effect between hypertrophic scar and keloid due to small sample size.

Conclusion

This is the first study that demonstrated the efficacy of fractional 1,550-nmerbium-doped fiber laser in treating keloids and hypertrophic scars which showed mild to moderate improvement. The effect of topical calcipotriol has no statistical difference from placebo. The future study for efficacy of vitamin D supplementation should be explored.

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