UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO
Facultad de Medicina
División de Estudios de Posgrado

Secretaria de Salud de la Ciudad de México
Centro Dermatológico “Dr Ladislao de la Pascua”

KERATOSIS PILARIS TREATMENT: EVIDENCE FROM INTERVENTION STUDIES

T E S I S

Para obtener el grado de especialista en

D E R M A T O L O G Í A

Presenta

Dr. Irvin Suástegui Rodríguez

Asesores

Martha Alejandra Morales Sánchez

Dr. Fermín Jurado Santa Cruz

Dra. María Luisa Peralta Pedrero

Ciudad de México; 2021

Review

KERATOSIS PILARIS TREATMENT: EVIDENCE FROM INTERVENTION STUDIES

Irvin Suástegui-Rodríguez, MD;[1] Laura Haydeé Camacho-Rosas, MD;[1] María Luisa Peralta-Pedrero, MD, MSc;[1] Fermín Jurado-Santa Cruz, MD;[1] Martha Alejandra Morales-Sánchez, MD, MSc[1]

1. Research and Education Unit, Centro Dermatológico “Dr. Ladislao de la Pascua”, Mexico City, Mexico.

CORRESPONDING AUTHOR: Martha Alejandra Morales-Sánchez, MD, MSc.

Research and Education Unit, Centro Dermatológico “Dr. Ladislao de la Pascua”, Mexico City, Mexico.

José María Vertiz Aveneu #464, Buenos Aires, Cuauhtémoc, Mexico City, Postal Code 06780, Mexico.

Telephone: (55) 18645848 / 55387033

E-mail: marthamoralessanchez@gmail.com

ABSTRACT

Keratosis pilaris is a common dermatosis seen in daily dermatologic practice. The diagnosis is clinical and is usually asymptomatic, although sometimes patients may complain of mild pruritus and its cosmetic appearance. Few reports exist about treatment. There are clinical trials assessing topical treatments and laser surgery, but we found no systematic reviews in the literature about its management. We have conducted an online research to identify evidence-based recommendations. Lactic acid, salicylic acid, and the 1064 nm Nd:YAG laser seem to be the most effective and safe treatments for keratosis pilaris among patients 12 years old and older; however, high-quality randomized controlled trials with long-term outcomes are needed.

INTRODUCTION

Keratosis pilaris (KP) is a common dermatosis, colloquially known as “chicken skin”. [1].It usually begins in the first decade of life, affects up to 40% of the population, and seems to affect women more than men (61% vs. 39%) [2,3].

KP is characterized by small, folliculocentric, keratotic papules that may have surrounding erythema. These lesions have a stippled appearance, resembling gooseflesh. The disorder tends to affect the extensor aspects of the arms, but it can also be present on thighs, face, and buttocks. Patients with KP are usually asymptomatic,

and patient complaints are related to the cosmetic appearance with occasional mild pruritus [2, 4].

The diagnosis is clinical, but dermatoscopy may be helpful in confirming the diagnosis and monitoring a therapeutic response [1]. Dermatoscopic findings include vellus hairs that are frequently twisted or coiled, being surrounded by peripilar casts. Groups of two to three hairs may emerge together. In a more severe presentation, vellus hairs are coiled and embedded in the horny layer. There may be perifollicular erythema and hyperpigmentation. These findings correlate with the classic histopathologic findings of distention of the follicular orifice by a keratinous plug containing one or more twisted hairs [5].

A family history is present in 39% of patients, indicating a potential genetic etiology with autosomal dominant inheritance, but the pathophysiology is unknown. One hypothesis proposes that the keratotic infundibular plug found in KP results from abnormal keratinization of the follicular epithelium. Another report noted that hair shafts extracted with a needle retained their coiled shape despite the removal from the follicle. Consequently, these authors hypothesized that KP is not a primary disorder of keratinocytes but rather a hair shaft or infundibular disorder. KP can occur when coiled hair shafts rupture the follicular epithelium and cause defective follicular keratinization and inflammation. One theory suggests the absence of sebaceous glands to explain both the abnormal keratinization and the hair shaft abnormalities in the early stages. [1].

Many agents have been employed in the treatment of KP, but few reports exist about the use of urea, retinol, tazarotene, calcipotriol, pulsed dye laser, and chemical peels [6-12]. Unfortunately, the quality of these studies is low due to its methodology (mainly case reports, case series, and letters to the editor). Clinical trials assessing topical treatments and laser surgery exist, but there are no systematic reviews in the literature about KP management or suggested standard of treatment. As a result, we conducted online research to identify the highest quality review papers to perform a systematic that might yield evidence-based recommendations.

METHODS

We performed this study at Centro Dermatológico “Dr. Ladislao de la Pascua” from November 1st, 2018 to March 31st, 2020, according to the Cochrane Handbook for Systematic Reviews of Interventions Version 6.0. The report adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and it was registered in the International Database of Prospective Register of Systematic Reviews (PROSPERO) on October 2nd, 2018 (ID: CRD42018111399) [13, 14].

Search strategy

We conducted our research on Scopus, Ovid, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Literatura Latinoamericana y del Caribe en Ciencias de la

Salud (LILACS) and Scientific Electronic Library Online (SciELO) with restriction to contributions published in English and Spanish but with no date restrictions. Search terms included "keratosis pilaris," "topical treatment," and "laser". Filters for "clinical trial" were applied, and duplications were removed.

Selection criteria

Eligible contributions comprised original blinded or non-blinded randomized and non-randomized clinical trials, which assessed topical or laser treatments in adults and children older than 12 years old with clinical or histopathologic diagnosis of KP. We excluded epidemiologic studies, reviews, case-control studies, case series , single-arm trials, and papers published in a language other than English or Spanish.

Data extraction

Titles and abstracts of the papers were screened independently by two review authors (Dr. Suástegui and Dr. Camacho) to identify those that potentially met the inclusion criteria. The full text of these potentially eligible studies was independently assessed by them and selected or rejected based on the inclusion and exclusion criteria. Any disagreement over the eligibility of particular studies was resolved through discussion with a third reviewer (Dr. Morales). A standardized pre-piloted form, designed by another team member (Dr. Peralta), was used to extract data from the included studies for assessment of study quality and evidence synthesis. Two review authors (Dr. Suástegui and Dr. Camacho) extracted data independently, and discrepancies were resolved

through discussion with a third author (Dr. Morales). Outcome measures reviewed included physician-assessed response to treatment and adverse events.

Risk of bias and quality assessment

We assessed the risk of bias with the Cochrane Risk of Bias tool, and the quality of the studies with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [14, 15].

RESULTS

Our electronic research identified 99 papers. After duplicates were removed and exclusion criteria were applied, we evaluated 16 titles and abstracts, of which 13 required full-text assessment. Finally, we included in our qualitative analysis eight papers published from 2013 to 2020 (Figure 1).

Four reports came from Thailand [16-19], two from Egypt [20, 21], and two from the United States of America [22,23]. Five contributions were double-blinded clinical trials, and the other three were evaluator-blinded. In three studies, one arm was randomized to be treated, and the other served as control [16, 18, 22]; two compared with placebo, and only one had three arms of intervention [21]. The youngest patient included was 13 years old and the oldest 65 years old.

We evaluated four studies as low-quality randomized clinical trials, mainly due to missing data related to the allocation sequence generation in the randomization process and blinding of the included subjects, notwithstanding the absence of intention to treat analysis of the lost participants [16, 18, 20, 21]. The remainder of the studies were assessed as moderate-quality randomized clinical trials, because the authors did not make intention to treat analysis [17, 19, 22, 23] (Table 1). Two publications had an unclear risk of bias in the randomization process, while all of them had a low risk of bias in the remaining four items. (Table 2 & Figure 2)

All of the studies assessed the intervention on the upper extremities. One of them evaluated the response on the thighs, too [20], and another included the effect on the abdomen, back, buttocks, and face [21]. In six papers, clinical improvement was assessed by a dermatologist using the Investigator's Global Assessment scale or a quartile grading scale (<25%, 25-50%, 50-75%, and >75%). (Tables 3 & 4)

TOPICAL TREATMENT

Salicylic acid and lactic acid

In one study, the effect of 10% lactic acid with 5% salicylic acid was compared. Participants employed the one designated agent twice daily on each of their extensor surface of the arms by using one hand to apply one test medication to the opposite treatment area and vice versa. Compared with baseline, both treatments showed a statistically significant reduction of lesions at the end of 4, 8, and 12 weeks of treatment ($P < 0.05$). The mean difference between both groups from baseline until the end of 12 weeks was 14%, which was statistically significant ($P < 0.05$), and favored the lactic acid group. Even the adverse events were more common in the lactic acid group than in the salicylic acid group, it was not statistically significant [17].

Epidermal microflora restoration

It has been proposed that restoring the skin microbiome with the ammonia-oxidizing bacteria (AOB), *Nitrosomonas utropha*, could raise nitric oxide levels and normalize keratinocyte proliferation and therefore ameliorate keratosis pilaris. The enrolled subjects received two identical white spray bottles: one bottle contained a placebo vehicle, while the other held the AOB. After four weeks of treatment, results demonstrated more reductions in the total amount, total surface area, and the maximum height of KP papules than the placebo, which was statistically significant. The investigators reported no adverse events [23].

.

LASER

In a single-blinded clinical trial, patients were treated in one arm with long-pulsed 1064 nm Nd: YAG laser, while the contralateral arm served as the control. The laser parameters included: spot size 15 mm, pulse width 30 msec, and a fixed fluence of 34 J / cm2; DCD was set at 20/20. Patients received three consecutive treatments at 4-week intervals. No anesthesia was used, the control arm received no sham irradiation, and emollients were not allowed. The mean global improvement score was superior compared with the control (1.12 ± 0.99 vs 0.59 ± 0.79, p = 0.007). The mean improvement in erythema and the number of papules were statistically significant (p = 0.009) [16].

In another study, the authors performed a split-body trial. The 810-nm pulsed diode laser was applied at a fluence of 45 to 60 J/cm2 (depending on Fitzpatrick skin type) and a pulse duration of 30 to 100 milliseconds, with precise settings selected to be just below the patient's threshold for purpura. Each treatment session entailed two nonoverlapping passes separated by a 1-minute delay. At follow-up, the median redness score was the same in both arms. The median overall score (combining erythema and roughness/bumpiness) favored the laser (p = .005) [22].

Fractional CO2 laser therapy was tested, using a 10,600nm eCO2 laser in a single session treatment. The settings were: pulse energy of 24–30 mJ and spot density of 300 spots/cm2 in static mode; 2 passes were delivered using a 300-density tip. At four

weeks after treatment, grade 2 or more improvement was achieved in four treated-arms and 1 in not treated-arm (p = 0.097). At 12 weeks of follow-up, six arms on the intervention side achieved grade 2 or more improvement, but no KP lesion on the control side achieved such response (p = 0.02). None of the patients experienced worsening of the lesions (Table 1). In terms of the mean improvement score, it was 0.90 (±0.97) on the treated side and 0.45 (±0.60) on the non-treated side B (p = 0.08) at four weeks after treatment. The mean improvement scores on side A and side B at 12 weeks of follow-up were 0.7 (±1.03) and 0.2 (±0.41), respectively (p = 0.05) [18].

In another clinical trial, the authors randomized only one arm of each participant and divided it into upper and lower parts (25 cm2 each). One part was randomized to be treated with three passes of FRAC3 1064 nm Nd: YAG laser while the other part received sham irradiation. The laser parameters were as follows: spot size 6 mm, pulse width 1.6 msec, and fixed fluences of 25 J / cm2. The mean percent change in the Subjects' Global Improvement Score (GIS) was 52.17% (95% CI 43.6, 60.74). No adverse events developed in any subjects after treatment sessions [19].

In a recent contribution, participants were assigned to two groups: one with bilateral KP on the arms, and another one with bilateral KP on the thighs. The patients in each group were again randomized into two groups. The right or left side of each patient randomly received laser treatment (power 12 W, time on 3 ms, PPI 5) in the form of two sessions fractional CO2 laser therapy four weeks apart and the contralateral right or left control

side was treated with topical 10% urea. The investigators observed good to excellent improvement on the arms and minimal to moderate on the thighs. None of the control subjects showed any improvement [20].

The investigators from another study assigned three areas. Area A was treated with fractional CO2 laser; area B was treated with fractional CO2 followed immediately by the Q-switched Nd:YAG laser (1064 nm), and the third area was treated with Q-switched Nd:YAG laser (1064 nm) alone. Each patient received a session every other week for three weeks. Results were very similar among the three groups. Only one patient reported hypopigmented macules in areas B and C, which improved after one month [21].

DISCUSSION

Whether it is an abnormal keratinization process or a body hair shaft disorder, KP is one of the most common dermatologic conditions seen in daily practice. KP may be confused with a larger number of dermatoses including Darier disease, pityriasis rubra pilaris, atopic dermatitis, lichen nitidus, eruptive vellous hair cysts, acne, and folliculitis [3]. Various treatments have been reported including urea, retinol, tazarotene, calcipotriol, pulsed dye laser, and chemical peels; however, few have been assessed in randomized clinical trials.

Because it often presents in patients with atopic dermatitis as an atopic stigma, and some authors have even reported filaggrin null mutations in patients with KP [24, 25], the first non-pharmacological approach to the disease is to ameliorate skin barrier function. We recommend that the patients bathe once daily for no more than 10 minutes with warm water, use a fragrance-free non-soap cleanser, and use of a moisturizer [26].

Based on the extracted data, lactic acid seems to be the most efficient therapy for KP in the extremities, but there are no data for its use in the face. We recommend it as the initial pharmacological approach, and it should be applied in the morning and before going to sleep on the affected skin for an indefinite period of time. Compared with the other treatment options, it achieves the highest percentage of improvement from baseline, it is a low-cost drug, and it has almost no adverse effects. Lactic acid belongs to the alpha-hydroxy acids (AHAs). This term was introduced to dermatology for the first time in 1974 when it was described as a useful medication for the severe hyperkeratosis of ichthyosis. Since then, AHAs have been found beneficial for topical treatment of dry skin, rough skin, dandruff, callus, acne, keratoses, warts, wrinkles, and photoaging skin [27]. The smallest of the AHA is the 2-carbon molecule, glycolic acid; next in size is lactic acid, which comes from the milk, with a 3-carbon chain [28]. All AHA cause detachment of keratinocytes in low concentrations by promoting the degradation of corneodesmosomes, thereby accelerating stratum corneum turnover [28]. Although the mechanism of action is not fully understood, it has been proposed that the topical application of AHA leads to a decrease in the calcium ion concentration in the epidermis; this reduction causes a loss of calcium ions from the cell junctions, leading directly to

desquamation. These properties have also been attributed to lactic acid [29, 30], which may explain its positive effects on KP.

In the last century, the improvement in hygiene practices and overall cleanliness has resulted in the near elimination of cutaneous commensal ammonia-oxidizing bacteria. These microorganisms produce nitric oxide and nitrite products through the oxidization of ammonia in sweat. Nitric oxide is a ubiquitous gas that functions as a signaling and effector molecule that regulates keratinocyte proliferation, and its healthy physiologic levels in the skin result in decreased keratinocyte proliferation [23]. Based on this, Lee and her coworkers tested ammonia-oxidizing bacteria. Nevertheless, it seems to be less effective than salicylic acid; thus, topical 5% salicylic acid applied twice daily could be considered a second-line topical therapy in patients that do not tolerate lactic acid or are lacking response to it.

Salicylic acid (SA) is obtained from the bark of the willow tree *Salix alba* but is also available synthetically [31]. SA was first described as a β-hydroxy acid, but later it was classified as a phenolic aromatic acid based on its chemical structure [32]. It extracts integral proteins from the desmosomes, including desmogleins, and subsequently destroys the cohesion of epidermal cells. Furthermore, it is reported to produce denaturation of membrane-crossing glycoproteins and fragmentation of corneodesmosomes. Therefore, the term 'desmolytic' has been proposed as being preferable to the term 'keratolytic' concerning the mechanism of action of salicylic acid

[28]. By causing the keratinocytes to separate from the follicular infundibulum, it could allow the release of the keratin plugs and the hair shaft, which explains its therapeutic effect on KP.

Lasers apply an electric charge that activates a medium that releases light, which is absorbed by skin chromophores (melanin, hemoglobin, water, tattoo ink). The absorbed energy is converted to thermal energy and the chromophore heats [33]. Based on the theory of the hair shaft alteration, probably the beneficial effects of laser are due to the destruction of the abnormal hair that consequently prevents the destruction of the hair follicular and inflammation.

Among lasers, the 1064 nm Nd:YAG laser, but not the Q-switched 1064 nm Nd:YAG laser, appears to be the most effective concerning positive changes in the evaluator´s assessment; thus, it should be considered as the first laser option in those patients that do not respond to topical drugs or even in combination them. Besides, the authors of the studies report few to no adverse effects and no dyschromia in skin phototypes III and IV. Patients must receive one monthly session for at least 4 months to achieve adequate response.

In refractory cases, the fractional carbon dioxide laser might be the next step in the KP management. We regard the 810-nm pulsed diode laser as a third option, considering it

improved the skin texture, but there were no differences in the erythema compared with no treatment.

Finally, we consider it is relevant for the purposes of this systematic review to mention some treatments assessed by different authors (whose articles were not included in our qualitative analysis for not meeting the inclusion criteria) because they may be useful in the future as a fundament for further studies. Clinical trials aimed at determining the efficacy and safety of new topical treatments and light-based therapies have been performed, obtaining promising results. Topical tacrolimus ointment 0.1% and Aquaphor® ointment have been compared in children 2 to 16 years old, reporting them as useful perhaps due to their antinflammatory effect and in ameliorating cutaneous barrier. Few to no adverse effects were reported by the authors during the four-week trial [34]. Photopneumatic therapy has been tested with average investigator-assessed improvement of 27% in erythema and 56% in skin texture roughness. Average patient self-reported improvement was 52% in erythema and 53% in skin texture. The mean satisfaction score was 6.3 on a scale of 1 to 10 (median 7.5) and 8 out of 10 participants reported they would choose to receive it again in the future [35]. A chlorine dioxide complex cleanser has proven to be useful due its keratolytic and antimicrobial properties [36]. In a recent study, intense pulsed-light was effective in reducing erythema and skin roughness [37].

CONCLUSIONS

Even keratosis pilaris is not a life-threatening condition, patients continue to ask for medication, which is why in this systematic review we summarized the available evidence in the scientific literature, and we have made some treatment suggestions. Nevertheless, it is crucial to conclude that high-quality randomized controlled trials on well-defined participants with long-term outcomes are necessary to determine the duration of response and its impact on the quality of life.

ACKNOWLEDGMENTS Lourdes Alonzo-Romero, MD, and Karla Leticia Valdés Morales, MD, from Centro Dermatológico “Dr Ladislao de la Pascua” assisted in the preparation of the manuscript.

REFERENCES

1. Wang JF, Orlow SJ. Keratosis Pilaris and its Subtypes: Associations, New Molecular and Pharmacologic Etiologies, and Therapeutic Options. Am J Clin Dermatol. 2018;19:733-757.
2. Poskitt L, Wilkinson JD. Natural history of keratosis pilaris. Br J Dermatol. 1994;130:711-713.
3. Chu AC, Teixeira F. Acquired Disorders of Epidermal Keratinization. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, eds: *Rook’s Textbook of Dermatology*. Chichester, West Sussex, UK: Wiley-Blackwell; 2016: 87.1-87.30.
4. Hwang S, Schwartz RA. Keratosis pilaris: a common follicular hyperkeratosis. Cutis. 2008;82:177-180.

5. Panchaprateep R, Tanus A, Tosti A. Clinical, dermoscopic, and histopathologic features of body hair disorders. J Am Acad Dermatol. 2015;72(5):890-900.
6. Novick NL. Practical management of widespread, atypical keratosis pilaris. J Am Acad Dermatol. 1984;11:305-306.
7. Standlee TL, Tindall JP. Clinical trials with topical vitamin A acid. South Med J. 1971;64:1496-1502.
8. Gerbig AW. Treating keratosis pilaris. J Am Acad Dermatol. 2002;47:457.
9. Kragballe K, Steijlen PM, Ibsen HH, et al. Efficacy, tolerability, and safety of calcipotriol ointment in disorders of keratinization. Results of a randomized, double-blind, vehicle-controlled, right/left comparative study. Arch Dermatol. 1995;131:556-560.
10. Kaune KM, Haas E, Emmert S, Schön MP, Zutt M. Successful treatment of severe keratosis pilaris rubra with a 595-nm pulsed dye laser. Dermatol Surg. 2009;35:1592-1595.
11. Schoch JJ, Tollefson MM, Witman P, Davis DM. Successful Treatment of Keratosis Pilaris Rubra with Pulsed Dye Laser. Pediatr Dermatol. 2016;33:443-446.
12. Reserva J, Champlain A, Soon SL, Tung R. Chemical Peels: Indications and Special Considerations for the Male Patient. Dermatol Surg. 2017;43 Suppl 2:S163-S173.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 2009;339:b2535.

14. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.
15. Aguayo-Albasini JL, Flores-Pastor B, Soria-Aledo V. Sistema GRADE: clasificación de la calidad de la evidencia y graduación de la fuerza de la recomendación [GRADE system: classification of quality of evidence and strength of recommendation]. Cir Esp. 2014;92:82-88.
16. Saelim P, Pongprutthipan M, Pootongkam S, Jariyasethavong V, Asawanonda P. Long-pulsed 1064-nm Nd:YAG laser significantly improves keratosis pilaris: a randomized, evaluator-blind study. J Dermatolog Treat. 2013;24:318-322.
17. Kootiratrakarn T, Kampirapap K, Chunhasewee C. Epidermal permeability barrier in the treatment of keratosis pilaris. Dermatol Res Pract. 2015; Epub 2015 Feb 24.
18. Vachiramon V, Anusaksathien P, Kanokrungsee S, Chanprapaph K. Fractional Carbon Dioxide Laser for Keratosis Pilaris: A Single-Blind, Randomized, Comparative Study. Biomed Res Int. 2016; Epub 2016 May 9.
19. Maitriwong P, Tangkijngamvong N, Asawanonda P. Innovative 1064-nm Nd:YAG Laser Significantly Improves Keratosis Pilaris, A Randomized, Double-Blind, Sham-Irradiation-Controlled Trial. Lasers Surg Med. 2019; Epub 2019 Nov 11.
20. Ismail S, Omar SS. Clinical and dermoscopic evaluation of fractional carbon dioxide laser in management of keratosis pilaris in Egyptian type skin. J Cosmet Dermatol. 2020;19:1110-1120.

21. Sobhi RM, Adawy NAH, Zaky IS. Comparative study between the efficacy of fractional CO2 laser, Q-switched Nd:YAG laser (1064 nm), and both types in treatment of keratosis pilaris. Lasers Med Sci. 2020; 35:1367-1376.
22. Ibrahim O, KhanM, Bolotin, D, et al. Treatment of keratosis pilaris with 810-nm diode laser: a randomized clinical trial. JAMA Dermatol. 2015;151:187-191.
23. Lee NY, Ibrahim O, Khetarpal S, et al. Dermal Microflora Restoration With Ammonia-Oxidizing Bacteria Nitrosomonas Eutropha in the Treatment of Keratosis Pilaris: A Randomized Clinical Trial. J Drugs Dermatol. 2018;17:285-288.
24. Brown SJ, Relton CL, Liao H, et al. Filaggrin null mutations and childhood atopic eczema: a population-based case-control study. J Allergy Clin Immunol. 2008;121:940-946.
25. O'Regan GM, Sandilands A, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. J Allergy Clin Immunol. 2009;124(3 Suppl 2):R2-R6.
26. McAleer MA, O'Regan GM, Ivine AD. Atopic dermatitis. In: Bolognia Jean, Jorizzo Joseph L.Schaffer, Julie V. eds *Dermatology*. 4th ed. Philadelphia: Elsevier Saunders; 2012: 208-227.
27. Yu RJ, Van Scott EJ. Alpha-hydroxyacids and carboxylic acids. J Cosmet Dermatol. 2004;3:76-87.
28. Wolverton Stephen E: Comprehensive Dermatologic Drug Therapy. Philadelphia: Saunders; 2013.
29. Wang X. A theory for the mechanism of action of the alpha-hydroxy acids applied to the skin. Med Hypotheses. 1999;53:380-382.

30. Smith WP. Epidermal and dermal effects of topical lactic acid. J Am Acad Dermatol. 1996;35:388-391.
31. Lin AN, Nakatsui T. Salicylic acid revisited. Int J Dermatol. 1998;37:335-342.
32. Arif T. Salicylic acid as a peeling agent: a comprehensive review. Clin Cosmet Investig Dermatol. 2015;8:455-461.
33. Habif Thomas P: Clinical dermatology a color guide to diagnosis and therapy. St. Louis, Missouri: Elsevier; 2016.
34. Breithaupt AD, Alio A, Friedlander SF. A comparative trial comparing the efficacy of tacrolimus 0.1% ointment with Aquaphor ointment for the treatment of keratosis pilaris. Pediatr Dermatol. 2011;28:459-460.
35. Ciliberto H, Farshidi A, Berk D, Bayliss S. Photopneumatic therapy for the treatment of keratosis pilaris. J Drugs Dermatol. 2013;12:804-806.
36. Zirwas MJ, Fichtel J. Chlorine Dioxide Complex Cleanser: A New Agent With Rapid Efficacy for Keratosis Pilaris. J Drugs Dermatol. 2018;17:554-556.
37. Maitriwong P, Tangkijngamvong N, Asawanonda P. Intense Pulsed-light Therapy Significantly Improves Keratosis Pilaris: A Randomized, Double-blind, Sham Irradiation-controlled Trial. J Clin Aesthet Dermatol. 2019;12:E53-E57.