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ORIGINAL ARTICLE

Efficacy and Safety of Calcipotriol/Betamethasone Dipropionate Ointment for the Treatment of Trachyonychia: An Open-Label Study

Jung-Min Park[1], Hyun-Ho Cho[2], Won-Jeong Kim[1], Je-Ho Mun[2], Margaret Song[1], Hoon-Soo Kim[1], Hyun-Chang Ko[2,3], Byung-Soo Kim[1,4], Moon-Bum Kim[1,4]

[1]Department of Dermatology, Pusan National University School of Medicine, [2]Department of Dermatology, Pusan National University Yangsan Hospital, [3]Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, [4]Bio-Medical Research Institute, Pusan National University Hospital, Busan, Korea

Background: Despite efforts to treat trachyonychia, there is no promising treatment modality. **Objective:** This study evaluated the efficacy and safety of calcipotriol plus betamethasone dipropionate ointment on trachyonychia. **Methods:** A total of 39 patients with 432 nails affected by trachyonychia were enrolled. All patients applied calcipotriol/betamethasone ointment once daily without occlusion for 6 months. Outcome measures were assessed by physician's global assessment (degree of roughness: 0, clear; 1, mild; 2, moderate; 3, marked; 4, severe) at all time points. **Results:** After 6 months of therapy, 98.6% (426/432) of nails showed significant clinical improvement; 4.2% were completely free from nail lesions. The mean physician global assessment score decreased significantly from 3.5 to 1.7 points ($p < 0.05$). No serious side effects were reported, except mild pruritus and erythema in 2 patients. **Conclusion:** This is the first study to prospectively evaluate the efficacy and safety of calcipotriol/betamethasone ointment for the treatment of trachyonychia. The results indicate topical calcipotriol/betamethasone is an effective and safe treatment for symptom improvement of trachyonychia. **(Ann Dermatol 27(4) 371~375, 2015)**

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Corresponding author: Moon-Bum Kim, Bio-Medical Research Institute, Pusan National University Hospital, Department of Dermatology, Pusan National University School of Medicine, 179 Gudeok-ro, Seo-gu, Busan 602-739, Korea. Tel: 82-51-240-7338, Fax: 82-51-245-9467, E-mail: drkmp@hanmail.net

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INTRODUCTION

Trachyonychia is characterized by excessive longitudinal ridging that gives the surface of the nail plate a rough appearance. It results from multiple foci of defective keratinization of the proximal nail matrix. The most common histopathologic findings of trachyonychia are spongiosis and exocytosis of inflammatory cells in the nail epithelia[1]. Although idiopathic trachyonychia may be much more common than reported[1], it may present with various associated skin or mucosal diseases including alopecia areata, lichen planus, psoriasis, and eczema[2]. It is also uncommonly reported in vitiligo and incontinentia pigmenti[3-6].
Trachyonychia predominantly occurs in children, although it can affect people of all ages[1]. Trachyonychia can improve spontaneously but may have a chronic course exceeding 6 years and result in cosmetic handicaps[2]. However, the treatment for trachyonychia remains challenging, because the disease tends to be refractory; no standardized therapeutic regimen exists. Therefore, this prospective open-label study evaluated the efficacy and safety of an ointment consisting of calcipotriol plus betamethasone dipropionate for the treatment of trachyonychia.

MATERIALS AND METHODS

Patients

Thirty-nine patients with trachyonychia who visited the Dermatologic Clinic of Pusan National University Hospital were enrolled. All patients underwent KOH examination to rule out onychomycosis. If a patient had clinical signs suggestive of dermatophytes or candidal onychomycosis, such as subungual hyperkeratosis, nail thickening, and/or discoloration, fungal culture was performed even though if the KOH examination result was negative. Patients with positive KOH test results or fungus cultures were excluded. Patients were also excluded if they currently used any systemic agents that could affect the nails had severe renal failure or hepatic failure, had other dermatological problems, were pregnant or lactating, or had a known hypersensitivity to a study molecule. The wash-out period was 12 weeks in patients treated with prior topical or systemic medications.

Methods

This prospective open-label trial was performed from September 2009 to October 2011. The study was approved by the Ethics Committee of Pusan National University Hospital (IRB No. C-1210-008-011), and voluntary written informed consent was obtained from all patients prior to participation.

Patients applied the calcipotriol plus betamethasone dipropionate ointment (Daivobet; LEO Pharma A/S, Ballerup, Denmark) once daily onto the proximal nail fold without occlusion for 6 months. Clinical outcomes were assessed at baseline and 1, 2, 3, and 6 months after treatment initiation. There is no objective clinical assessment index for trachyonychia, so we established the "severity index of trachyonychia." The suggested grading system is as follows: stages 0, I, II, III, and IV indicate no involvement, mild roughness, moderate roughness, marked roughness, and severe roughness, respectively (Fig. 1). We evaluated the patients according to the physician global assessment (PGA) using the severity index of trachyonychia. A complete response (CR) was defined as no involvement of trachyonychia, and a partial response (PR) was defined as an improvement of more than 1 PGA stage. All adverse events that occurred during treatment were recorded.

Statistical analysis

Paired t-tests were performed to evaluate the significance of differences in the outcome measures during treatment period by using predictive PASW Statistics ver. 18.0 for Windows (IBM Co., Armonk, NY, USA). The level of significance was set at $p<0.05$.

RESULTS

Among the 47 total patients, 39 (83.0%) completed the 6-month study. Eight patients dropped out owing to poor compliance. These 39 patients, including 14 men and 25 women (age range, 3～68 years; mean, 35.7 years), had a total of 432 nails affected by trachyonychia at baseline (264 fingernails and 168 toenails). The mean disease duration was 49.0 months (range, 1～240 months).

The mean±standard deviation PGA score decreased significantly from baseline to the end of treatment (3.5±0.8 to 1.7±0.9, respectively, $p<0.05$). PGA scores decreased consistently throughout treatment (3.1±1.0, 2.3±0.9, and 2.1±0.9 at 1, 2, and 3 months, respectively) (Fig. 2).

At baseline, 30 (6.9%), 147 (34.0%), and 255 (59.0%) patients were in stage II, III, and IV, respectively. Among stage II cases, 10.0% (3/30) and 90.0% (27/30) of nails showed CR and PR, respectively, after 2 months of

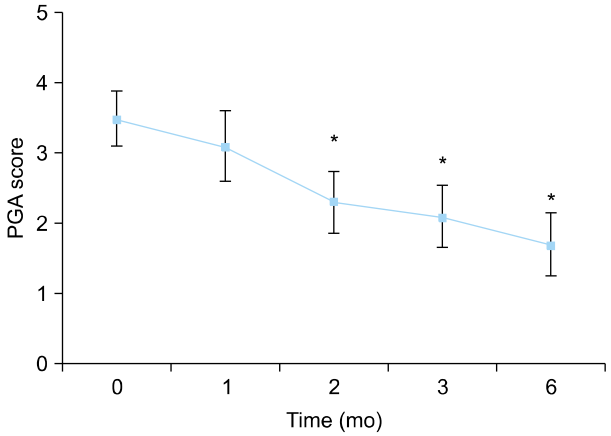

Fig. 2. Temporal changes of mean physician global assessment (PGA) score (*$p<0.05$ vs. baseline).

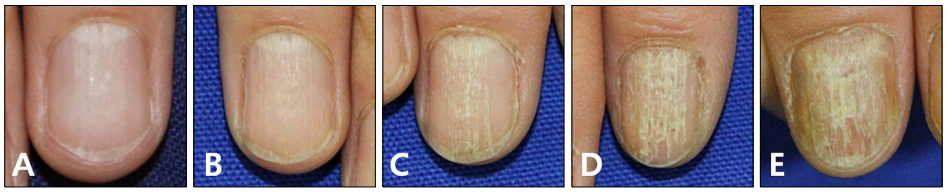

Fig. 1. Severity index of trachyonychia: (A) stage 0, (B) stage I, (C) stage II, (D) stage III, (E) stage IV.

therapy. Among stage III cases, 89.1% (131/147) and 6.8% (10/147) of nails achieved CR and PR, respectively, at the end of treatment. Among stage IV cases, all nails achieved PR after 1 month of therapy, and 2.0% (5/255) achieved CR at the end of treatment (Table 1).

At the end of treatment, 18 (4.2%) nails achieved CR, and 195 (45.1%), 131 (30.3%), and 88 (20.3%) were in stage I, II, and III, respectively (Fig. 3). After 1 month of therapy, 38.7% (167/432) of the nails achieved PR. After 2 months of therapy, 0.7% (3/432) and 93.3% (403/432) of the nails achieved CR and PR, respectively. After 3 months of therapy, 0.7% (3/432) and 94.9% (410/432) of the nails achieved CR and PR, respectively. At the end of treatment, 4.2% (18/432) and 94.4% (408/432) of the nails achieved CR and PR, respectively (Table 1, Fig. 4).

Two (5.2%) patients experienced adverse effects: mild pruritus and erythema in 1 patient (2.6%) each; both were transient and self-limited. There were no serious side effects or discomfort that caused patients to stop treatment.

DISCUSSION

Trachyonychia is a self-limiting condition but may occasionally require intervention[7]. Nevertheless, the long-term follow-up study of Sakata et al.[2] indicates trachyonychia lasting more than 6 years and childhood onset are unlikely to recover without treatment. They also report that patients without any improvement of their nails do not develop accompanying skin or mucosal disease. Thus, idiopathic trachyonychia usually has a chronic course and in-

Table 1. Summary of treatment results

	1 Month	2 Months	3 Months	6 Months
Stage II (n=30)				
PR	18 (60.0)	27 (90.0)	27 (90.0)	27 (90.0)
CR	0 (0.0)	3 (10.0)	3 (10.0)	3 (10.0)
Stage III (n=147)				
PR	81 (55.1)	121 (82.3)	128 (87.1)	131 (89.1)
CR	0 (0.0)	0 (0.0)	0 (0.0)	10 (6.8)
Stage IV (n=255)				
PR	68 (100.0)	255 (100.0)	255 (100.0)	250 (98.0)
CR	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.0)
Total (n=432)				
PR	167 (38.7)	403 (93.3)	410 (94.9)	408 (94.4)
CR	0 (0.0)	3 (0.7)	3 (0.7)	18 (4.2)

Values are presented as number (%). PR: partial response, CR: complete response.

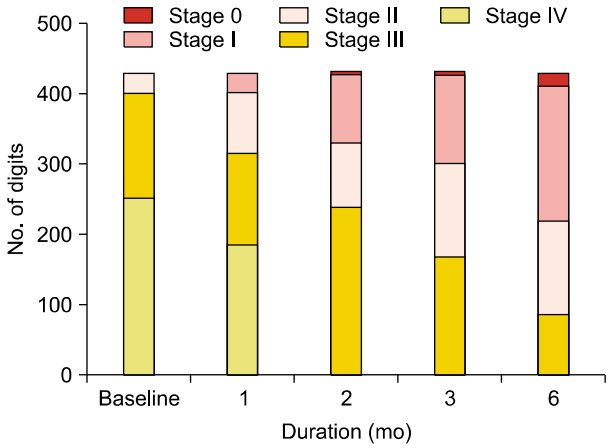

Fig. 3. Temporal changes of physician global assessment score (n=432 nails).

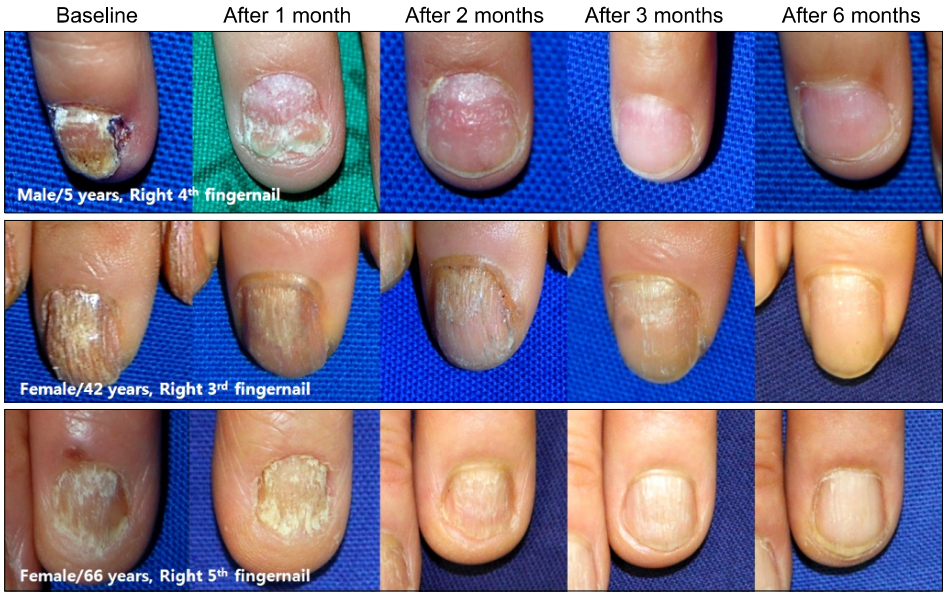

Fig. 4. Temporal changes of trachyonychia after calcipotriol/betamethasone dipropionate ointment.

curs cosmetic problems.

Treatment for trachyonychia is often unsatisfactory, and there is no single evidence-based treatment for the disease. Topical corticosteroids have been widely used, and other treatment modalities include topical tazarotene gel and 5-fluorouracil, systemic corticosteroids, retinoids, and cyclosporine, psoralen plus ultraviolet A, and intralesional injection of triamcinolone into the proximal nail fold[8-14].

Calcipotriol plus betamethasone dipropionate ointment is primarily used to treat psoriasis[15]. Regarding nail disorders, another study evaluated the efficacy of calcipotriol plus betamethasone dipropionate ointment for the treatment of nail psoriasis[16]. Nail psoriasis was assessed using the nail psoriasis severity index; there was a 72% overall improvement after 3 months of treatment. Therefore, we used calcipotriol plus betamethasone dipropionate ointment to treat trachyonychia in the present study.

Trachyonychia is classically classified into 2 groups:[17,18] (1) severe trachyonychia, in which the nail is ridged, rough, deprived of its natural luster, and has a "sand paper-like" texture in the longitudinal direction; (2) mild trachyonychia, in which the nail plate is shiny with numerous closely aggregated small superficial pits. However, this classification is insufficient for assessing the clinical severity of trachyonychia, because the clinical appearance of trachyonychia exhibits a wide spectrum of severity. To our knowledge, there is no clinical grading system for trachyonychia. Therefore, we created the grading system used in present study. The mean PGA score at baseline was 3.5 ± 0.8, decreasing significantly to 1.7 ± 0.9 at 6 months.

Among stage II, III, and IV trachyonychia cases, 90.0%, 82.3%, and 100% achieved PR after only 2 months, respectively. These findings suggest stage II, III, and IV trachyonychia exhibit a relatively early response to treatment. After 6 months of treatment, the CR rates in stage II, III, and IV nails were 10.0% (3/30), 6.8% (10/147), and 2.0% (5/255), respectively. These results suggest the CR rate is higher in mild cases than severe cases. However, an additional treatment modality may be required to achieve CR in trachyonychia exceeding stage II.

No large-scale study has evaluated the treatment of trachyonychia, making it difficult to compare the efficacy of calcipotriol/betamethasone ointment with other agents[1,8-14]. In a previous study, 4 children with nail pitting received an intralesional injection of triamcinolone into the proximal nail fold and exhibited a 42% reduction of pitting at 4 months[11]; however, the maximum effect was observed at 2 months, and the improvement was only temporary. The authors state that this indicates the inflammatory process in the nail matrix is ongoing and that the anti-inflammatory effect of intralesional steroid is only transient.

In the 2 histological studies of clinically idiopathic trachyonychia in 44 patients, 28 (63.6%) patients exhibited spongiotic change, 9 (20.5%) showed psoriasiform changes, and 6 (13.6%) showed typical features of nail lichen planus[18,19]. Calcipotriol/betamethasone ointment can be used for patients with psoriasis, lichen planus, or eczematous dermatitis, although it is rarely used for the latter 2 diseases[20,21]. The present results suggest calcipotriol/betamethasone ointment exerts a direct therapeutic effect to modulate the inflammatory reaction of the nail dystrophy and normalize the abnormal differentiation of keratinocytes in the nail matrix and nail plate. In addition, petrolatum-based ointments can act as occlusive agents, which could help reduce nail roughness and improve symptoms; this could explain the relatively early response after 1～2 months of treatment in the present study.

Trachyonychia is a chronic condition that requires long-term treatment. Topical corticosteroid monotherapy for this condition may not be safe, because the long-term topical application of these drugs may result in atrophy of the nails or even focal bone resorption[22]. Meanwhile, topical calcipotriol is not associated with any of the side effects of corticosteroids, and its combined use with a topical corticosteroid results in a steroid-sparing effect. Conversely, topical corticosteroids may suppress the local cutaneous irritation caused by topical calcipotriol[23]. In the present study, only 1 patient (2.6%) each had a mild itching sensation and transient erythema at the application site.

The limitations of this study are that fungal cultures were performed only for patients who had clinical signs suggestive of dermatophytes or candidal onychomycosis. It would be better to perform fungal cultures for all patients to rule out onychomycosis. Furthermore, there were no data about recurrence or conditions after treatment cessation. Considering environmental factors can differ between fingernails and toenails, and that a topical agent is easier to apply to fingernails, the treatment response could be better in fingernails than toenails. However, we did not assess the therapeutic response of fingernails and toenails separately.

This is the first study to prospectively evaluate the efficacy and safety of calcipotriol/betamethasone ointment for the treatment of trachyonychia. We hypothesized that calcipotriol/betamethasone ointment is effective for treating trachyonychia because of its effectiveness for treating psoriatic nails. The ointment improved the condition of 98.6% (426/432) of the nails with trachyonychia, 4.2% (18/432) of which exhibited total clearance after 6 months.

Thus, the results suggest topical calcipotriol/betametha-

sone ointment is an effective and safe treatment for trachyonychia that can be used as monotherapy. In addition, the severity index of trachyonychia described herein, which is based on the roughness of trachyonychia lesion in the involved nail, is an easy and fast assessment that can be used in clinical practice. Nevertheless, further double-blinded and placebo-controlled studies are required to confirm the effectiveness of calcipotriol/betamethasone ointment for the treatment of trachyonychia.

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REFERENCES

1. Gordon KA, Vega JM, Tosti A. Trachyonychia: a comprehensive review. Indian J Dermatol Venereol Leprol 2011;77:640-645.
2. Sakata S, Howard A, Tosti A, Sinclair R. Follow up of 12 patients with trachyonychia. Australas J Dermatol 2006;47:166-168.
3. Peloro TM, Pride HB. Twenty-nail dystrophy and vitiligo: a rare association. J Am Acad Dermatol 1999;40:488-490.
4. Khandpur S, Reddy BS. An association of twenty-nail dystrophy with vitiligo. J Dermatol 2001;28:38-42.
5. Khandpur S, Bansal A, Sharma VK, Bhatti SS, Singh MK. Twenty nail dystrophy in vitiligo. J Dermatol 2007;34:189-192.
6. Scardamaglia L, Howard A, Sinclair R. Twenty-nail dystrophy in a girl with incontinentia pigmenti. Australas J Dermatol 2003;44:71-73.
7. Sehgal VN. Twenty nail dystrophy trachyonychia: an overview. J Dermatol 2007;34:361-366.
8. Soda R, Diluvio L, Bianchi L, Chimenti S. Treatment of trachyonychia with tazarotene. Clin Exp Dermatol 2005;30:301-302.
9. Schissel DJ, Elston DM. Topical 5-fluorouracil treatment for psoriatic trachyonychia. Cutis 1998;62:27-28.
10. Halkier-Sørensen L, Cramers M, Kragballe K. Twenty-nail dystrophy treated with topical PUVA. Acta Derm Venereol 1990;70:510-511.
11. Khoo BP, Giam YC. A pilot study on the role of intralesional triamcinolone acetonide in the treatment of pitted nails in children. Singapore Med J 2000;41:66-68.
12. Tosti A, Piraccini BM, Cambiaghi S, Jorizzo M. Nail lichen planus in children: clinical features, response to treatment, and long-term follow-up. Arch Dermatol 2001;137:1027-1032.
13. Brazzelli V, Martinoli S, Prestinari F, Borroni G. An impressive therapeutic result of nail psoriasis to acitretin. J Eur Acad Dermatol Venereol 2004;18:229-230.
14. Piérard GE, Piérard-Franchimont C. Dynamics of psoriatic trachyonychia during low-dose cyclosporin A treatment: a pilot study on onychochronobiology using optical profilometry. Dermatology 1996;192:116-119.
15. Park JY, Rim JH, Choe YB, Youn JI. Comparison of calcipotriol monotherapy and a combination of calcipotriol and methylprednisolone aceponate therapy in psoriasis patients. Ann Dermatol 2003;15:60-63.
16. Rigopoulos D, Gregoriou S, Daniel Iii CR, Belyayeva H, Larios G, Verra P, et al. Treatment of nail psoriasis with a two-compound formulation of calcipotriol plus betamethasone dipropionate ointment. Dermatology 2009;218:338-341.
17. Baran R, Dawber RPR, Richert B. Physical signs. In: Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, editors. Diseases of the nails and their management. 3rd ed. Oxford: Blackwell Science, 2001:67-69.
18. Tosti A, Bardazzi F, Piraccini BM, Fanti PA. Idiopathic trachyonychia (twenty-nail dystrophy): a pathological study of 23 patients. Br J Dermatol 1994;131:866-872.
19. Grover C, Khandpur S, Reddy BS, Chaturvedi KU. Longitudinal nail biopsy: utility in 20-nail dystrophy. Dermatol Surg 2003;29:1125-1129.
20. Theng CT, Tan SH, Goh CL, Suresh S, Wong HB, Machin D; Singapore Lichen Planus Study Group. A randomized controlled trial to compare calcipotriol with betamethasone valerate for the treatment of cutaneous lichen planus. J Dermatolog Treat 2004;15:141-145.
21. Basak PY, Ergin S. Comparative effects of calcipotriol and betamethasone 17-valerate solution in the treatment of seborrhoeic dermatitis of the scalp. J Eur Acad Dermatol Venereol 2001;15:86-88.
22. Wolf R, Tur E, Brenner S. Corticosteroid-induced 'disappearing digit'. J Am Acad Dermatol 1990;23:755-756.
23. Lebwohl M. Topical application of calcipotriene and corticosteroids: combination regimens. J Am Acad Dermatol 1997;37:S55-S58.