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Research Article

COMPARISON OF THE EFFICACY OF TOPICAL CLOBETASOL PROPIONATE 0.05% CREAM, ORAL METHOTREXATE AND ORAL ACITRETIN IN NAIL PSORIASIS

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A B S T R A C T

Background: Prevalence of nail psoriasis among plaque psoriasis patients documented in the literature is over 50%, with an estimated lifetime incidence of 80-90%. Prevalence of isolated nail psoriasis is 5-10%.

Materials and Methods: This open label randomized study was conducted on patients of nail psoriasis. Patients were randomized into Group A (topical clobetasol propionate 0.05% cream under occlusion, once daily application) Group B (oral methotrexate 0.3mg/kg/week) and group C (oral acitretin 0.3mg/kg/day). Patients were followed-up after 4, 8 and 12 weeks, to measure improvement in Nail Psoriasis Severity Index (NAPSI), nail matrix and nail bed scores.

Results: All three drugs individually showed significant improvement in NAPSI and nail matrix scores. While improvement in nail bed score were significant in methotrexate (P=0.024) and acitretin (P=0.005) groups only. On inter groups comparison there was significant difference between group A and group B in the improvement of NAPSI (P=0.044) and nail matrix scores (P=0.024). No significant difference between group A and C, and Group B & C. While improvement in nail bed score was insignificant between groups.

Conclusions: All therapies were significantly effective and methotrexate was superior to topical clobetasol 0.05% cream in the improvement of NAPSI and nail matrix scores.

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INTRODUCTION

Psoriasis is a chronic skin disease that causes significant distress and morbidity. Prevalence of nail psoriasis among plaque psoriasis patients documented in the literature is over 50%, with an estimated lifetime incidence of 80–90%.[1] Nail psoriasis in the absence of cutaneous or joint disease is present in 5–10% cases.[2] Nail psoriasis leads to considerable impairment in quality of life due to aesthetic concerns and more importantly limitations in daily activities resulting from the associated pain.[3,4]

Nail psoriasis may show different clinical presentations according to the structure that is involved within the nail apparatus. All signs of nail psoriasis are not specific and may be found in several other nail conditions. Therefore, histology of involved tissue is the gold standard for making the diagnosis of nail psoriasis. Signs that are highly suggestive for nail psoriasis include irregular pitting, salmon coloured patches on the nail bed and onycholysis with erythematous borders.

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Nail psoriasis often produces other non specific nail abnormalities including splinter haemorrhages, nail bed hyperkeratosis, nail thickening & crumbling, paronychia and rarely, leukonychia, red spot in the lunula and trachyonychia.
Although nail psoriasis is common, the results of treatment of nail psoriasis are often disappointing and to the best of our knowledge there is no comparative study between topical clobetasol and systemic drugs. We present herein comparative efficacy of clobetasol propionate 0.05% cream, with two oral medicines.

MATERIALS AND METHODS

This open label randomized study was conducted at a tertiary health care centre from November 2015 to June 2017. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all patients. The study group comprised patients of nail psoriasis (with and without other types of psoriasis) who fulfilled the following inclusion criteria: age >12 years, in isolated nail psoriasis cases having nail pittings >60, no systemic treatment for 1 month & no topical treatment for one week, and KOH negative for fungus. In two patients with only nail changes and pitting <60, biopsy were taken to confirm the diagnosis.

For acitretin group, patients with pregnancy and lactation, women of childbearing potential who cannot guarantee adequate contraception during & up to 3 years (and up to 3 months in methotrexate group) of treatment, dyslipidemia, pancreatitis, alcoholic, history of taking hepatotoxic drug & jaundice and patients with psoriatic arthritis were excluded. For methotrexate group, patients with pregnancy and lactation, women of childbearing potential, alcoholic, history of taking hepatotoxic drugs and jaundice, Hb < 8gm/dl, TLC < 4000 cells/cumm, Platelet count < 1 lakh/cumm, lymphocytes < 1500 cells/cumm, raised aminotransferases (>2 times of the upper limit of normal range), raised bilirubin more than 30% of baseline, any sign of infection, tuberculosis and immunosuppression or any chronic disease, renal failure, peptic ulcers and unreliable patients were excluded from the study.

The sample size is calculated with prevalence of nail psoriasis 5% (level of confidence 95%) and absolute error 5%, which permits the sample size of 80 cases. The dropout rates assuming to be 10%, the final sample size will be 88 which were approximated to 90 cases. Computer-generated random number table was used for randomization with 1:1 allocation to divide the patients equally into following three groups: Group A (topical clobetasol propionate 0.05% cream under occlusion, once daily application) Group B (oral methotrexate 0.3mg/kg/week) and group C (oral acitretin 0.3 mg/kg/day). Study period per subject was of 12 weeks.

A thorough clinical examination, detailed history, NAPSI, nail matrix and nail bed scores, routine investigations like complete blood count, liver function test, kidney function test, and fasting lipid profile were done at the first visit. Patients were followed at 4, 8, and 12 weeks to evaluate improvement in NAPSI, nail matrix and nail bed scores & for side effects if any. At every visit clinical and laboratory parameters were noted. If however during study, the patient develop any of the above mentioned exclusion criteria, then we stopped the treatment and patient was switched on some other alternative treatment.

The various parameters studied during observation period were presented in the form of Mean ± SD for quantitative variables and number & percentage were used for qualitative variables. Student t-test and Kruskal-Wallis test followed by post hoc Dunn's test were used for the comparison of mean values as per their suitability and applicability. Chi-square test was used for proportions. The critical value of '*P*' indicating the probability of significant difference was taken as <0.05 and < 0.001 as highly significant for intra & inter groups comparisons. The data was analyzed using software SPSS version 16.0.

RESULTS

This study was carried out in 90 patients of nail psoriasis attending outpatient department, 72 of these were males and 18 females. Out of 90, ten patients were excluded either due to side effects or who lost to follow-up. There was no significant difference in distribution of age of patients (*P*=0.744), age of disease onset (*P*=0.722) and total duration of disease (*P*=0.162) among the groups. Out of 80, fifty-four (67.5%) patients have associated plaque and palmoplantar psoriasis while isolated nail psoriasis was present in 26 (32.5%) patients.

Table 1 Patients Characteristics

Total no. of patients enrolled	90
Male patients	72 (80%)
Female patients	18 (20%)
Patient with associated plaque or palmo-planter psoriasis	61 (67.77%)
Isolated nail psoriasis patients	29 (32.22%)
Mean age ± S.D. (yrs)	33.76±15.66
Mean age of disease onset ± S.D. (yrs)	28.42±14.29
Mean duration of disease ± S.D. (yrs)	5.14±4.98
Mean base line NAPSI ± S.D.	25.83±9.09
Mean base line nail matrix score ± S.D.	22.17±10.69
Mean base line nail bed score ± S.D.	3.63±6.97
Mean base line no. of pitting ± S.D.	73.26±66.68

Table 2 Improvement in NAPSI

Group	Baseline	Follow up at 1 month	Follow up at 2 month	Follow up at 3 month	Intra group comparison
Group A (n=30)	27.00±8.19	26.72±8.28	24.03±7.63	19.80±7.04	t=9.378 *P*<0.001
Group B (n=27)	25.66±10.86	24.47±11.46	22.13±9.43	15.66±9.10	t=5.539 *P*<0.001
Group C (n=23)	27.17±7.73	26.78±7.22	22.86±7.00	16.30±6.30	t=11.319 *P*<0.001
(Kruskal Wallis test)	χ2=1.053 *P*=0.591	χ2=1.521 *P*=0.468	χ2=0.857 *P*=0.652	χ2=4.449 *P*=0.108	
Post Hoc test comparison	A vs B (*P*=0.581) A vs C (*P*=0.945) B vs C (*P*=0.560)	A vs B (*P*=0.380) A vs C (*P*=0.982) B vs C (*P*=0.393)	A vs B (*P*=0.400) A vs C (*P*=0.606) B vs C (*P*=0.757)	A vs B (*P*=0.044) A vs C (*P*=0.102) B vs C (*P*=0.769)	

Table 3 Improvement in nail matrix score

Groups	Baseline	Follow up at 1 month	Follow up at 2 month	Follow up at 3 month	Intra group comparison
Group A (n=30)	24.90±9.50	24.62±9.57	21.93±8.81	18.06±8.05	t=8.820 *P*<0.001
Group B (n=27)	20.70±12.12	19.39±12.34	17.56±11.78	12.92±9.96	t=5.418 *P*<0.001
Group C (n=23)	23.73±8.41	23.30±7.93	19.69±7.20	14.60±6.75	t=9.852 *P*<0.001
(Kruskal Wallis test)	χ2=2.301 *P*=0.317	χ2=2.804 *P*=0.246	χ2=2.414 *P*=0.299	χ2=5.405 *P*=0.067	
Post Hoc test comparison	A vs B (*P*=0.125) A vs C (*P*=0.682) B vs C (*P*=0.297)	A vs B (*P*=0.067) A vs C (*P*=0.641) B vs C (*P*=0.192)	A vs B (*P*=0.101) A vs C (*P*=0.398) B vs C (*P*=0.445)	A vs B (*P*=0.024) A vs C (*P*=0.143) B vs C (*P*=0.484)	

Table 4 Improvement in nail bed score

Groups	Baseline	Follow up at 1 month	Follow up at 2 month	Follow up at 3 month	Intra group comparison
Group A (n=30)	2.10±4.01	2.10±4.08	2.10±4.08	1.73±3.35	t=1.943 *P*=0.062
Group B (n=27)	4.96±8.83	4.68±8.81	4.37±7.82	2.74±5.99	t=2.402 *P*=0.024
Group C (n=23)	3.43±6.43	3.47±6.61	3.17±6.10	1.69±4.09	t=3.089 *P*=0.005
(Kruskal Wallis test)	χ2=1.599 *P*=0.449	χ2=1.620 *P*=0.445	χ2=1.553 *P*=0.460	χ2=0.273 *P*=0.872	
Post Hoc test comparison	A vs B (*P*=0.109) A vs C (*P*=0.471) B vs C (*P*=0.421)	A vs B (*P*=0.161) A vs C (*P*=0.463) B vs C (*P*=0.535)	A vs B (*P*=0.180) A vs C (*P*=0.530) B vs C (*P*=0.500)	A vs B (*P*=0.411) A vs C (*P*=0.976) B vs C (*P*=0.426)	

Table 5 Adverse effects

Adverse effects	Group A (n=30)	Group B (n=30)	Group C (n=30)
Nausea	0	7	0
Vomiting	0	3	0
Headache	0	2	1*
Increased Bilirubin	0	1*	0
Transaminases > 2 times of normal range	0	1*	1*
Dyslipidemia	0	0	1*
Hypopigmentation around nail unit	6	0	0
Pain at proximal nail fold	0	1*	0
Menstrual disturbance	0	0	1*

*Excluded

At the end of study (12 weeks) mean percentage of improvement in NAPSI were 26.66%, 38.97% and 40% in group A, B and C respectively. All three groups showed significant improvement in NAPSI and nail matrix scores individually. While improvement in nail bed score was significant in methotrexate (*P*=0.024) and acitretin (*P*=0.005) groups only. On inter groups comparison there was significant difference between group A vs group B in the improvement of NAPSI (*P*=0.044) and nail matrix scores (*P*=0.024) & insignificant between group A vs C, and Group B vs C. While improvement in nail bed score was not significant between the groups [group A vs B (*P*=0.411), group A vs C (*P*=0.976), and group B vs C (*P*=0.426).

Hypopigmentation around nail unit was noticed in 6 patients (20%) of group A. In group B, 23% (7 patients) complained of nausea. Three patients (10%) developed vomiting. Two patients suffered from headache. Raised liver enzymes >2 times of the upper limit of normal range, jaundice and pain in distal phalynx was noted each in one patient. In group C, headache, dyslipidemia, menstrual disturbance and elevated transaminases were seen, each in one patient (Table 5).

DISCUSSION

Nail changes are frequent in psoriasis. These changes are seen in association with all types of psoriasis of the skin and are frequently present with psoriatic arthropathy.[5,6] Changes in nail varies from minor defects in nail plate (pits) to severe alteration of nail organ (onychodystrophy) and loss of nail plate (pustular psoriasis of nail). These morphologic alterations reflect the extent to which the psoriatic process affects the various portions of the nail organ. Nail organ consists of proximal nail fold, nail matrix, nail bed and hyponychium. Localization of psoriatic tissue changes at these sites and duration of these processes decide the degree of nail involvement.

Pitting is the most common nail abnormality seen in psoriasis.[7,8] Pits affect the fingernails more commonly than the toenails.[7] Psoriasis affecting the proximal nail matrix disrupts the keratinization of its stratum corneum by parakeratotic cells.[1] As the developing nail plate grows out beyond the margin of the proximal nail fold, the abnormal cells are lost to leave behind surface indentations that appear as pits.[9] The pits in psoriasis are often quite small (under 1 mm in diameter) and can be shallow or deep seated. Occasionally, isolated, large, deep, punched out areas (elkonyxis) producing holes in the nail plate are seen. Pits are often rather irregularly or randomly placed on one or more nails but at times there may be a regular and uniform pitting of all the nails in a grid-like pattern (thimble nails). More than 20 fingernail pits per person are suggestive of a psoriatic etiology and more than 60 pits per person are unlikely to be found in the absence of psoriasis.[10] Leukonychia occurs when psoriasis induced parakeratosis affects only the intermediate and ventral matrices that form the under-surface of a nail plate.[1,11] Nail plate thickening and crumbling suggests an extensive involvement of the entire nail matrix by the psoriatic process.

Nail bed involvement results in salmon patches, subungual hyperkeratosis, splinter hemorrhages, and onycholysis. Salmon patches clinically appear as circular areas of reddish-brown discoloration beneath the nail plate (oil drop sign) and are the result of focal nail bed parakeratosis.[12] Subungual hyperkeratosis is the consequence of abnormal cornification of the nail bed and hyponychium. Splinter hemorrhages are seen in the nail beds of 42% of finger nails and 6% of toe nails and are the equivalent of an Auspitz sign in the nail.[9,11] Increased vascularity and fragility of the nail bed together with trauma are responsible for this. Onycholysis results from psoriasis affecting the distal nail bed or hyponychium or extension of oil spots distally. It results from raising of the nail plate off the nail bed as a result of deposition of cells that have not undergone desquamation.[1] This accumulated tissue is friable and is liable to be infected by Candida and Pseudomonas leading to either yellow/green discoloration. Onycholysis may progress until much of the nail is separated from the nail bed.

The Nail Psoriasis Severity Index (NAPSI) has been developed as an objective and reproducible tool, which helps to estimate the nail involvement and therefore to standardize the treatment outcome assessments.[13] In our study we also assessed nail psoriasis severity using NAPSI score. Treatment of isolated nail psoriasis is difficult and often unsatisfactory. Information about the efficacy of treatments available for nail psoriasis is scarce because most studies on skin psoriasis do not focus on the nail changes. To the best of our knowledge there is no such comparative study from India.

In nail psoriasis, potent and super-potent corticosteroids are used frequently, and appear to be more effective in nail matrix psoriasis than in nail bed psoriasis. The frequency of application is usually once or twice daily. In our study we applied once daily clobetasol propionate 0.05 % cream, under occlusion, which showed significant improvement in nail matrix score (*P*<0.001) in comparison to nail bed score (*p*=0.062). Nakamura *et al.*[14] in 2012 compare clobetasol propionate at concentrations 0.05%, 1%, and 8% with placebo (coat nail lacquer) applied twice weekly for 4 months and showed 51% improvement in treatment group (8% clobetasol more efficient). In our study at the end of 3 months mean improvement in the NAPSI was 26.66% with clobetasol propionate 0.05% cream which is highly significant (p<0.001). In patients treated with clobetasol propionate 0.05% cream, hypopigmentation around nail unit was noticed in 6 patients (20%).

Methotrexate was approved by FDA for treatment of severe psoriasis in 1971.[15] It is still considered the gold standard for the treatment of psoriasis worldwide and was first systemic drug for psoriasis to be FDA approved. One RCT comparing methotrexate and cyclosporine in nail psoriasis showed a mean NAPSI improvement of 43 % in methotrexate-treated patients and 37 % in cyclosporine-treated patients at 24

weeks (not significant).[16] The methotrexate group showed a significant improvement in nail matrix scores only, while the cyclosporine group showed significant improvement in nail bed scores only.[16] Methotrexate efficacy to treat nail psoriasis has also been compared with briakinumab in a RCT.[17] Target NAPSI improved 38 % in methotrexate-treated patients and 56 % in briakinumab-treated patients at 30 weeks. Study by Sanchez-regna *et al*.[18] showed improvement in NAPSI 7%, 31% and 35% at 20, 30 and > 30 weeks respectively with methotrexate.

In patients treated with methotrexate, we got significant mean NAPSI improvement of 38.97 % (P<0.001) which is comparable with previous studies. Mean improvement in nail matrix score was 37.58 % which was highly significant (P<0.001) while improvement in nail bed score was significant (P =0.024).

In patients treated with methotrexate, 23% (7 patients) complained of nausea. Three patients (10%) developed vomiting. Nausea & vomiting was mild to moderate and improved on folic acid supplementation. Two patients suffered from headache. Raised liver enzymes >2 times of the upper limit of normal range, jaundice and pain in distal phalynx was noted each in one patient and these were excluded from the study.

In 1987, etretinate was approved by FDA for the treatment of psoriasis, but problems like long-term storage in fat led to its replacement with acitretin in 1997. With its more favorable pharmacokinetics (acitretin being 50 times less lipophilic than etretinate has significantly shorter elimination half-life) acitretin became an established systemic therapy for severe psoriasis.

The position of acitretin in the treatment of nail psoriasis is that of a rather slow-acting compound with moderate efficacy and action. Study by Tosti A *et al*.[19] reported mean percentages of reduction of the NAPSI score 41%. Our result is also comparable to this study as we got mean percentage improvement in NAPSI score of 44% (P<0.001). Sanchez regana *et al*.[18] reported improvement in NAPSI- 12 %, 41 % and 52 % at 12, 24, and 48 weeks respectively. Demirsoy *et al*.[20] reported 25 % improvement in NAPSI score 16 weeks with acitretin.

Mean percentage improvement of nail matrix score in acitretin group was 38.47 % which was highly significant (P<0.001). While mean percentage improvement in nail bed score was 50.72 % which was significant (P=0.005). In acitretin group, headache, dyslipidemia, menstrual disturbance and elevated transaminases were seen, each in one patient and these were also excluded from the study.

CONCLUSION

Thus, we conclude that all three groups individually show significant improvement in NAPSI and nail matrix score. While improvement in nail bed score was significant in methotrexate (P=0.024) and acitretin (P=0.005) groups only. On inter groups comparison there was significant difference between group A and group B in the improvement of NAPSI (P=0.044) and nail matrix score (P=0.024).

On further follow-up beyond study period 4 patients in methotrexate group and 6 patients in acitretin group completely cleared nail changes at 24 weeks, which favours the slightly higher efficacy of acitretin.

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