International Journal of Research in Dermatology
Somani SP et al. Int J Res Dermatol. 2022 Jan;8(1):101-109
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20214919

Original Research Article

Efficacy and safety of iontophoresis combined sodium salicylate in acquired plantar keratoderma-a randomized controlled study

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Received: 22 November 2021
Accepted: 17 December 2021

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ABSTRACT

Background: Palmoplantar keratoderma is a heterogenous group of disorders, hereditary or acquired, characterized by thickening of palms and soles. Though it is not a life-threatening condition, it affects individual's quality of life. As treatment of keratoderma has always been troublesome, upgraded treatment modalities which improves keratoderma efficiently are always encouraged.
Methods: In this randomized controlled study, patients of plantar keratoderma of age group of 18-65 years were randomly divided in group A and group B. In group A, iontophoresis combined sodium salicylate was offered to patients twice weekly for 8 weeks of duration, during which DC current was supplied at 5-15 mA for 10 min of duration. Whereas, in group B patients applied topical salicylic acid 12% ointment at home twice a day for 8 weeks.
Results: Our study of 70 patients of keratoderma, revealed diffuse (94%) pattern of involvement with female preponderance (55.7%) and occupation wise, most common among laborers (54.2%) followed by housewives (27.1%). Statistically significant number of patients showed reduction in severity grading of parameters, in both groups at end of 8 weeks. Same way, mean values of parameter grading significantly reduced at 8 weeks in both the groups. But intergroup values showed no significant difference. Mean EASI (Eczema Area Severity Index) score showed statistically significant reduction in group B as compared to group A at 8th week. Percentage of reduction of EASI score was also significantly higher in group B at end of treatment.
Conclusions: Here both treatment modalities are safe and effective, topical being slightly more efficacious than iontophoresis. So, we can conclude that no additional privilege of drug delivery through iontophoresis.

Keywords: Iontophoresis, Plantar keratoderma, Efficacy, EASI score

INTRODUCTION

Palmoplantar keratodermas (PPK) are a diverse entity of keratinization disorders characterized by abnormal thickening of the palms and soles.[1] They are traditionally divided into genetic[2] and acquired types.[3] Various Acquired PPKs have varying epidermal involvement patterns: diffuse, focal, punctate and transgradient.[3]

As the terms hyperkeratosis and keratoderma have been used interchangeably throughout the literature, we define acquired keratoderma as a non-hereditary hyperkeratosis of the palms and/or soles that involves ≥30% of the surface of involved acral areas and that may or may not be associated with clinical inflammation.[3]

Acquired PPK can be due to common causes like, keratoderma climactericum (menopause), drug related, malnutrition associated, chemically induced, systemic disease related, malignancy associated, dermatoses related, infectious, and idiopathic.[3]

Treatment of keratoderma remains problematic and restricted to symptomatic therapy. Topical therapies like keratolytic (such as urea, salicylic acid, and lactic acid), topical retinoids, topical corticosteroids and topical

psoralen and ultraviolet A phototherapy are showing variable results in the small database of keratoderma.[4]

Salicylic acid is widely and commonly used keratolytic compound. In addition to keratolytic action, it has anti pruritic [5], sun-protective, bacteriostatic as well bactericidal[6] actions. It has been included in many over the counter dermatological agents and has been widely used for plaque psoriasis, acne, corn, wart, pigmented lesions, seborrheic dermatitis, ichthyosis etc.[7] But in literature, case reports revealed mixed responses to topical salicylic acid in keratoderma.

Iontophoresis is a noninvasive, convenient and rapid method of delivering water soluble, ionized medication into skin. It allows higher concentration of drug to be delivered to a limited area with negligible side effects.[8]

Till now, there are only few studies evaluating clinical profile of palmoplantar dermatoses and only few case reports showing varied response to treatment. We could not find any study comparing efficacy of iontophoresis in keratoderma. In our study, we compared efficacy of iontophoresis combined aqueous solution of sodium salicylate with topical salicylic acid 12% ointment.

METHODS

After receiving approval from institutional review board and clinical trials registry India (CTRI) registration (CTRI/2019/09/021444) this randomized controlled study was undertaken during October 2018 to December 2019. Patients of either gender >18 years of age, clinically diagnosed as plantar keratoderma and had involvement of bilateral symmetrical plantar surfaces with >30% of area of each sole were included in the study. Sample size was calculated as 80 by using Openepi software with confidence interval 95% and power 80%. Then they were randomly allotted to group A (Iontophoresis) and group B (Topical) according to random number generator. We excluded patients with infective etiology of keratoderma, with pacemaker or bone plate, who had taken treatment within last 3 months, pregnant and lactating females.

A written informed consent was taken from all patients and a pre - set proforma was used to collect detailed history and demographic details. Certain Laboratory tests e.g., Complete blood count, renal and liver function tests, blood sugar level, thyroid function tests were ordered for every patient.

Group A (Iontophoresis)

Two square plastic trays are filled with this 12% aqueous solution of salicylate (by dissolving 12 gm of sodium salicylate powder in 100 ml tap water) and metal electrodes of iontophoresis were put in them. Patient was instructed to put both soles over electrodes in plastic tray. Then direct current was applied with gradually increasing intensity guided by mild tingling sensation felt by the patient. The maximum intensity was 10mA and the minimum was 5 mA. After 10 min, direction of current was reversed using switching arrangement and reversed current was applied with same intensity for 10 min. So, iontophoresis was applied within range of 5-10 mA for 20 min of duration. This procedure repeated twice a week for 8 weeks, covering total 16 sittings. Patient was counselled to apply emollient cream twice daily at home.

Group B (Topical)

The 12% salicylic acid ointment was applied twice daily, along with emollient cream at home. Patients were counselled to wash immediately if severe irritation occurs. Patients were followed up every 4 weeks for duration of 2 months. This regimen was continued till 8 weeks of duration. Patients from both groups were also given antihistamines for pruritus.

Outcome measures of study

Objective outcome measures

EASI (eczema area severity index) score, which is calculated at time of enrollment and then at 4th and 8th week.

The EASI score is the sum of severity grading of different parameters [1. Fissures 2. Hyperkeratosis 3. Erythema. 4.xerosis 5. Scaling] multiplied by Image J score. Image J software was used to measure area of involvement of plantar surfaces.

Parameter's severity grading is as follows: None [0] - absent, mild [1]-just perceptible, moderate [2]-obvious and severe [3]-very prominent.

For image j score calculation, 1-10 cm^2 graded as 1, 11-20 cm^2 graded as 2 and so on. Severity of image J score was decided as: None: no area of involvement, Mild: 1-4.5 score, Moderate: 4.6-9.0 score, Severe: 9.1-13.5 score. Clinical photographs by using canon SLR camera

Subjective outcome measures

Physician's global assessment score and patient's self-assessment score.

Statistical analysis of study

Data collected were analyzed in Graphpad Instat 3.0 software (California USA). All the quantitative parameters were expressed in Mean ± standard deviation (SD) frequencies (number of cases) and relative frequencies (percentages) when appropriate whereas categorical data given as number and percentages. Nonparametric tests were applied as the collected data were in non- Gaussian distribution. Mann–Whitney test was used for the comparison between two groups. Friedman test with Dunn's test was applied for

comparing different parameters same group. Chi square test was used to compare observed frequencies between groups. P<0.05 considered statistically significant.

RESULTS

A total of 81 patients of plantar keratoderma were screened during study period, out of them 73 met inclusion criteria and among them, 70 patients had completed 8 weeks of treatment as shown in Figure 1.

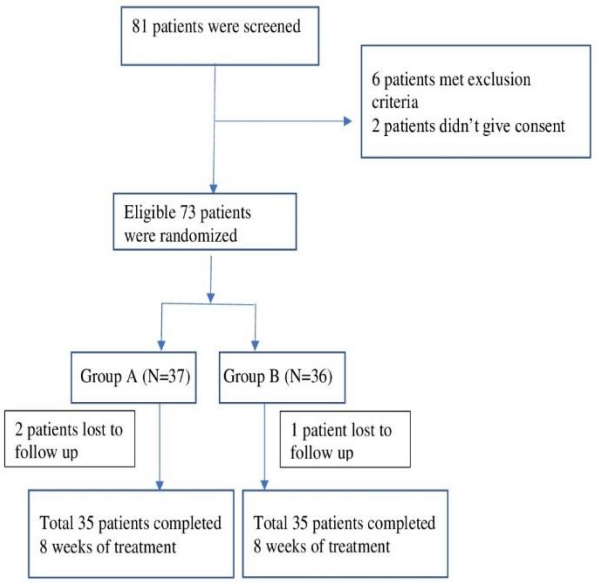

Figure 1: Flowchart of study.

As stated in table 1 age of patients in both groups ranged from 25-65 years (mean age was being 41.2). Most number of patients belonged to age group of 35-50 years (60%) and there were 39 females (55.7%) and 31 males (44.3%). Among associated conditions, maximum association was found with menopause (18.5%), followed by diabetes (10%), hypertension (8.5%), other dermatoses- psoriasis (7%) and hypothyroidism (3%).

A higher incidence of keratoderma was observed among laborers (54.2%) followed by housewives (27.1%). Also, greater number of patients showed exacerbation in winters (52.8%) as compared to summers (35.7%).

Out of 70 patients, there were 66 patients (94.2%) with diffuse keratoderma, whereas only 3 (4.2%) had focal keratoderma and 1 (1.4%) had trans-gradient pattern. 35 (50%) had duration of disease for 1-3 months, 17 (24.2%) had <1 month, 14 (21.4%) had 3-12 month and 5 (7.14%) had >12 month of duration. As depicted in table 2, statistically significant (p=0.004 and 0.001) higher mEASI (mean EASI) score among patients who had longer duration (>12 moths) of disease in both groups. Although, there was no significant (p>0.05) impact of disease duration on treatment response. Besides, as shown in Figure 2, greater the severity of keratoderma higher intensity of DC current required during treatment.

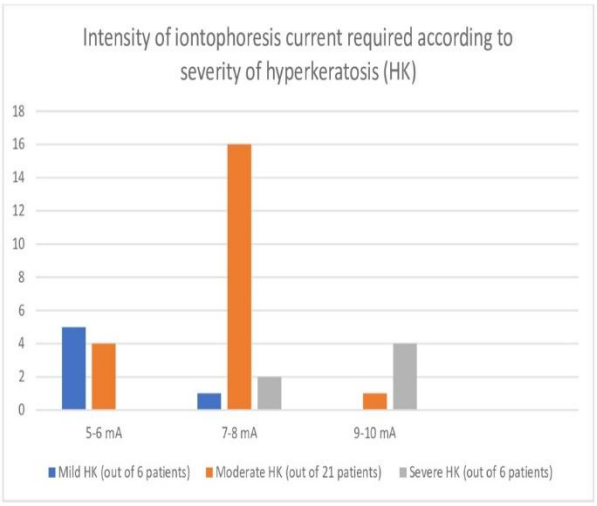

Figure 2: Column charts of number of patients according to severity of parameters in both groups at baseline and at 8th week.

Amid of associated symptoms, most common was pruritus present in 59 patients (84.2%) followed by pain in 50 (68.5%) and burning in 22 (31.4%). At end of 8th week, only 6 patients (12%) had pain, 3 had (13.6%) burning and 15 had (25.4%) pruritus. Here, pruritus was found to be relieved in significantly (p=0.003) higher number of patients in group A as compare to group B. Whereas, remission of pain and burning was comparable in both groups (p>0.05).

Evaluation parameters

As mentioned in methodology, we evaluated EASI score using 6 parameters: fissures, hyperkeratosis, xerosis, scaling, erythema and image J score. Among both groups, maximum improvement was found in hyperkeratosis. 64.2% of patients had nil hyperkeratosis, followed by fissures (52.8%), xerosis (47.1%) and scaling (20%) and image J score (7%).

As shown in Figure 3, significant number of patients shifted from higher grade (severe, moderate) to lower grade (mild, no disease) of severity at end of 8 weeks for all parameters in both groups.

But intergroup comparison of number of patients showing decrement of severity grading, was not statistically significant.

On comparing intra-group mean values of severity gradings of parameters in Table 3, extremely statistically significant reduction was there at 4th and 8th week in both groups (p<0.0001 using Friedman's test f/b Dunn's test) but inter-group comparison was not statistically

significant for any parameter (p>0.05 using Mann Whitney's test).

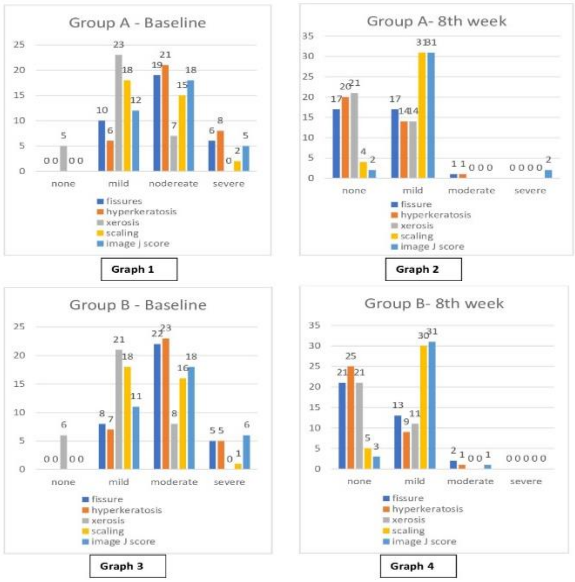

Figure 3: Comparison of intensity of iontophoresis according to severity of hyperkeratosis.

EASI score

As mentioned in table 4, intra-group reduction of mEASI was statistically significant at 4th and 8th weeks (p<0.0001 using Friedman's test f/b Dunn's test). Inter-group comparison also revealed significantly lower mEASI in group B as compared to group A at 8th week (p=0.03 using Mann Whitney's test). Besides, on comparing mean % of reduction of EASI score, significantly higher reduction was seen in group B as compare to A (p=0.03 using Mann Whitney's test) [Figure 4].

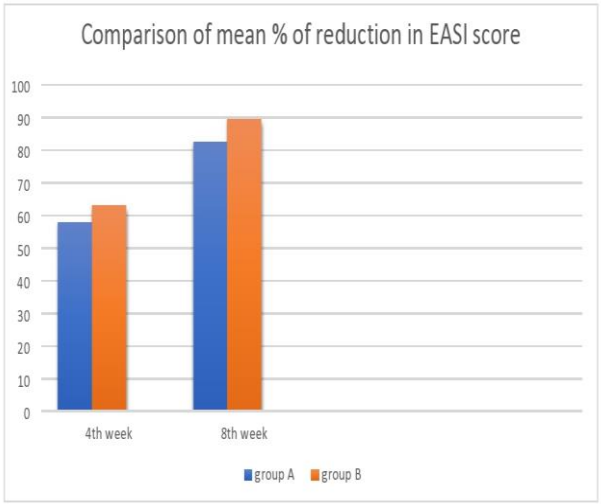

Figure 4: Comparison of mean % of reduction in EASI score between both groups.

Table 5 depicted about severity of keratoderma according to EASI score at baseline and 8th week. At time of enrollment, a total number of 12 patients had mild keratoderma, 28 had moderate keratoderma, 23 had severe keratoderma and 7 had very severe keratoderma. Whereas, at end of 8 weeks, only subtle keratoderma was found in 66 patients, only 2 had moderate and 2 had very severe keratoderma.

Physician's global assessment score [Figure 5] and patient's self-assessment score [Figure 6] were also compared at end of treatment between both groups but no any significant difference was found (p>0.05).

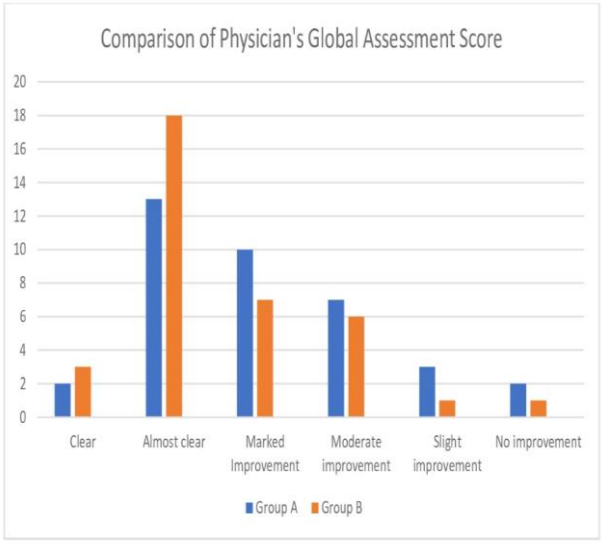

Figure 5: Comparison of physician's global assessment score.

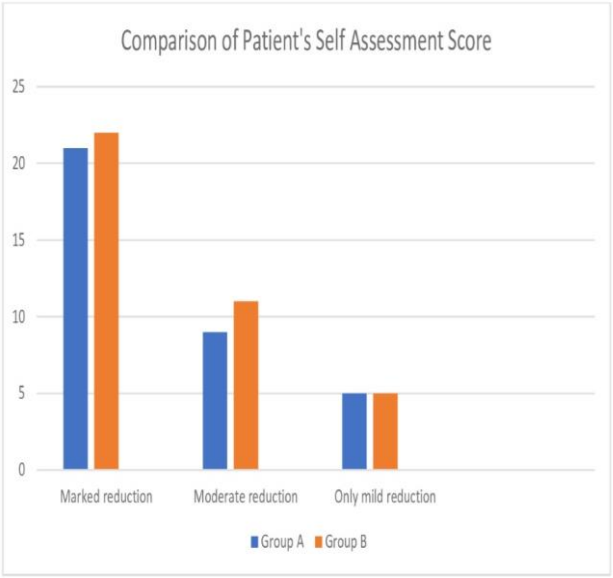

Figure 6: Comparison of patient's self-assessment score.

Side effect profile

An excessive tingling sensation among 34.2% of patients in group A, none in group B. There was aggravation of itching during treatment in 0.2% and 28.5% among group A and B respectively. 25.7% of patients from group A found difficulty to adhere treatment plan, none in group B. Whereas, signs of salicylism were not found in any single patient. Also followed up patients for duration of 2 months post-treatment, but no any recurrence was noted.

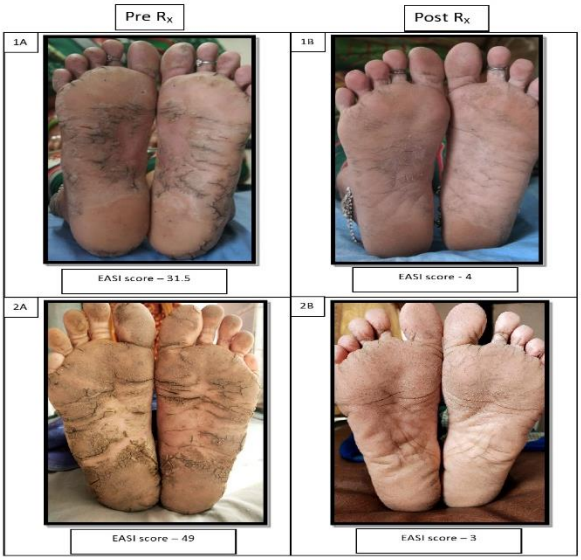

Figure 7: Pre and post treatment comparison of keratoderma in two patients (1A and 1B, 2A and 2B) of group A.

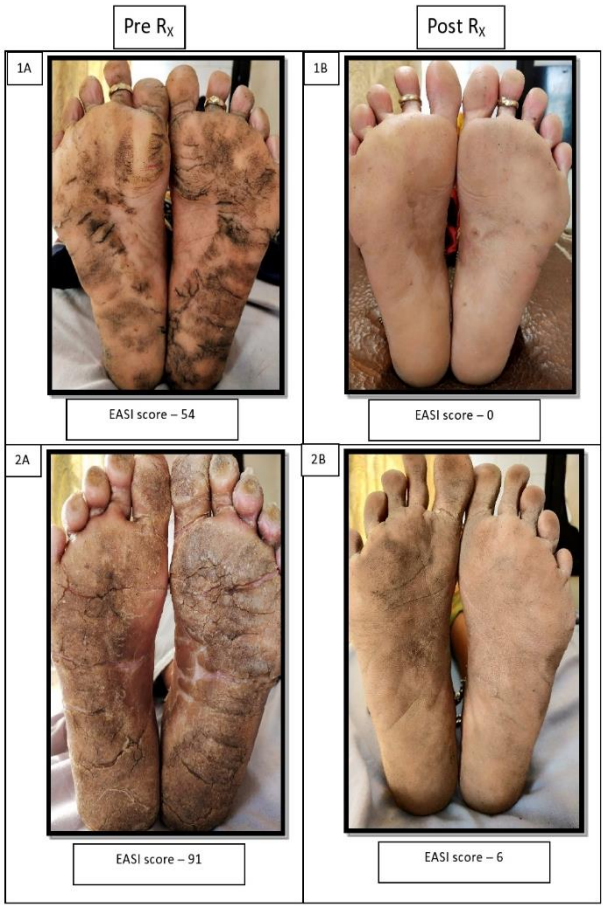

Figure 8: Pre and post treatment comparison of keratoderma in two patients (1A and 1B, 2A and 2B) of group B.

Table 1: Baseline characteristics of patients.

Variables	Group A, n (%)	Group B, n (%)	P (chi square test)
Mean Age ±SD	41.4±8.9	41.1±8.8	0.91
Gender distribution			
Male	15 (42.8)	16 (45.7)	0.83
Female	20 (57.2)	19 (54.3)	
Age distribution (Years)			
18-35	8 (22.8)	9 (25.7)	0.82
36-50	22 (62.8)	20 (57.1)	
>50	5 (14.2)	6 (7.1)	
Associated conditions			
Menopause	06 (17.1)	07 (20)	0.64
Diabetes mellitus	03 (8.5)	04 (11.4)	
Hypothyroidism	01 (2.8)	02 (5.7)	
Hypertension	03 (8.5)	03 (8.5)	
Other dermatoses	02 (8.5)	03 (5.7)	
Occupation			
Laborer	18 (51.4)	20 (57.1)	0.48
Housewife	09 (25.7)	10 (28.5)	
Other	08 (22.8)	05 (14.2)	
Seasonal exacerbation			
Winter	19 (54.28)	18 (51.4)	0.76
Summer	11 (31.4)	14 (40)	

P>0.05, not statistically significant.

Table 2: Comparison of impact of duration on severity of disease and on response to the treatment.

Duration	Group A (Mean ± SD)		Group B (Mean ± SD)	
	Baseline	8th week	Baseline	8th week
<1 month	35.3±15.1	3.7±2.1	21.7±4.8	2.5±1.0
1-3 month	33.8±13.2	3.7±4.8	32.8±11.4	2.2±1.0
4-12 month	58.1±22.0	5.6±2.2	66.7±15.1	4.8±2.1
>12 month	66.2±1.7	66.2±1.7	58.0±2.8	23.0±28.6
P (Friedman's test)	<0.004**	0.07	0.001**	0.1

**p value ≤0.001.

Table 3: Intra and inter group comparison of mean values of severity grading of parameters at baseline, 4th and 8th week.

Variables	0 week	4th week	8th week	P value (Friedman's test f/b Dunn's test)
Fissures (Mean ± SD)				
Group A	1.8±0.7#	1.1±0.5*	0.5± 0.5**	<0.0001
Group B	1.9±0.6#	1.1±0.3#	0.4±0.5**	<0.0001
P (Mann Whitney's)	0.80	0.60	0.42	
Hyperkeratosis (Mean ± SD)				
Group A	1.9±0.6**	1.1±o.4#	0.4±0.5**	<0.0001
Group B	2.0±0.6**	1.1±0.4#	0.3±0.5**	<0.0001
P value	0.50	0.86	0.69	
Xerosis (Mean ± SD)				
Group A	1.0±0.6*	0.6±0.5	0.4±0.4**	<0.0001
Group B	0.9±0.6*	0.4±0.5	0.3±0.4**	<0.0001
P value	0.49	0.46	0.53	
Scaling (Mean ± SD)				
Group A	1.4±0.6	1.0±0.3	0.8±0.3#	<0.0001
Group B	1.4±0.5#	0.9±0.2	0.8±0.3**	<0.0001
P value	0.85	0.53	0.83	
Area score (Mean ± SD)				
Group A	6.1±2.6**	4.3±2.6**	2.5±2.8**	<0.0001
Group B	5.9±2.3**	3.8±1.9**	1.6±1.4**	<0.0001
P value	0.75	0.48	0.06	

*- p≤0.05, # - p≤0.01, **- p≤0.001.

Table 4: Inter and intra group comparison of mean EASI score at baseline, 4th and 8th week.

Groups	EASI score mean ± SD			
	0 week	4th week	8th week	P (Friedman's test f/b Dunn's test)
Group A	41.6±20.51**	16.9±14.6**	8.02±15.2**	<0.0001
Group B	39.9±18.9**	14.9±10.0**	2.9±7.4**	<0.0001
P (Mann Whitney's)	0.74	0.40	0.03*	

*- p≤0.05, **- p≤0.001.

Table 5 Comparison of severity of keratoderma between both groups at baseline and at 8th week

EASI score severity	Number of patients			
	At baseline		At 8th week	
	Group A	Group B	Group A	Group B
Subtle (0-10)	00	00	32	34
Mild (11-20)	06	06	00	00
Moderate (21-40)	13	15	01	01
Severe (41-60)	12	11	00	00
Very severe (>60)	04	03	02	00
P (chi square test)	0.68		0.19	

P>0.05, not significant.

Table 6: Various case reports stating variable response of topical management.

Sources	Type of keratoderma	Topical treatment given	Response
Gupta et al[21]	Hereditary punctate PPK	Salicylic acid 12%	Mild improvement
Bukhari et al[22]	Hereditary puctate PPK	Salicylic acid 20% + urea 40%	Little improvement
Kiatsurayanon et al[23]	Linear punctate keratoderma	Salicylic acid 10% + urea 10%	Mild improvement
Kong et al[24]	Keratosis punctate palmoplantaris	Topical retinoids	Marked improvement
Gandhi et al[25]	Acral peeling + ppkd	Emollient + topical retinoid	No significant improvement
Osman et al[26]	Spiny keratoderma	Topical 5-FU	Marked improvement
Present study	Diffuse keratoderma	Salicylic acid 12% ointment	Excellent response

Table 7: Comparison of various case report/ series in means of efficacy of iontophoresis.

Source	Indication	Intensity and duration	Medication/ water	Result
Haseena et al[8]	Palmoplantar psoriasis	5-10 mA for 15 min	Methotrexate solution	Comparable with coal tar ointment
Mukherjee et al[19]	Hyperkeratosis	3-5 mA for 10-15 min	Sodium salicylate	Excellent results
Erichetti et al[27]	Aquagenic keratoderma	10-15 Ma for 15 min	Tap water	Remission induced
Zeinalzade et al[28]	Hyperhidrosis	12mA for 30 min	1% aluminium chloride	Mean reduction was 72%
DogrukKacar et al[29]	Paediatric hyperhidrosis	6.8-24 mA for 20 min	Tap water	50% or more reduction in sweating
Tupker et al[30]	Foot eczema	30mA for 30 min	Tap water iontophoresis f/b PUVA	No benefit of iontophoresis over PUVA
Sobhi et al[31]	Melasma	5 mA for 10 min	Vit C nanosomes	Significant improvement
Present study	Plantar keratoderma	5-10 mA for 20 min	Sodium salicylate	Excellent response

DISCUSSION

Palmoplantar keratoderma is a heterogenous group of keratinization disorder with hyperkeratotic thickening of palms and soles. Palmoplantar keratoderma poses minimum threat to patients in terms of mortality, but has capacity to affect individual's quality of life. Routine day to day activities are hampered which can also lead to loss of wages.

The current study revealed mean age of 41.42 years for acquired keratoderma and greater prevalence in middle age group (35-50 years), in concordance with studies done by Nair et al and Kodali et al.[9,10] There was female preponderance (55.7%) in present study, whereas Mahajan et al and Kodali et al observed male predominance.[9,10] Female preponderance in our study is probably because of exposure to various detergents, soaps and chemicals while doing washing and cleansing activities. Females, also who are engaged in outdoor work i.e., laborer are exposed to repeated mechanical friction, trauma additionally.[9,12] Furthermore, greater incidence of plantar keratoderma among laborers and exacerbation of plantar keratoderma more in winter (52.8%) than summer (35.7%) was in concordance with other studies.[9,10,19]

The present study reflected remarkable association with menopause (18.5%) due to female preponderance. Followed by, diabetes mellitus (10%), hypertension (8.5%) and hypothyroidism (4.2%). In literature, there were case reports potentiating the same.[13-17] Furthermore, 7% of patients had chronic plaque Psoriasis, as Palms and soles are usually involved in 3-5% cases of psoriasis.[9] As 94% of patients had diffuse pattern of involvement, we can accept it as commonest pattern for acquired keratoderma.

In the treatment aspect, apart from empirical management comprising systemic retinoids and topical keratolytics like salicylic acid and urea, newer physical modalities like CO2 laser and iontophoresis had also been used for keratodermas.[18,19] Although there are no any RCTs comparing any of treatment modalities, available in literature.

Salicylic acid in concentrations 5% and above, exerts a potent, deep and rapid keratolytic effect. Additionally, it

also comprises anti-inflammatory and antipruritic actions.[20] From the literature, various case reports depicting variable response to different topical agents in keratoderma were stated in Table 6.

Iontophoresis a recognized noninvasive therapeutic method for delivering water soluble ionized medication into the skin. It improves efficacy by continuous release and decreases the total dose and dosing frequency. Table 7 portrayed different case reports and pilot studies about efficacy of iontophoresis. As the different scoring system was used there, we could not compare our study variables with them.

In the present study, extremely significant number of patients showed reduction in severity grade of all parameters in both groups. But intergroup comparison was not statistically significant. In similar way, there was significant reduction in mean value of gradings of all parameters at 4th week and at 8th week in both groups. But intergroup comparison showed no statistically significant difference between groups. So, here it was found that both treatment modalities are highly effective in acquired keratoderma. Furthermore, we didn't find any case of contact dermatitis or signs of salicylism in any of our patients, so topical and iontophoresis both have proven their safety also.

But on analyzing EASI score, mean EASI score was significantly lower in group B as compared to A. Additionally, mean % of reduction in EASI score was higher in group B at 8th week. So, at the end, we can interpret that topical salicylic acid had higher efficacy as compared to iontophoresis and iontophoresis had not added any additional merits to patient.

Interestingly, present study showed better and earlier remission of pruritus in iontophoresis group as compared to topical. So, iontophoresis is more efficacious to remit pruritus as compared to topical. Besides, higher intensity of current (DC voltage) was required for more severe hyperkeratosis. So, intensity of current was directly proportional to thickness of soles. As these observations were not defined earlier in literature, more future studies require to potentiate the same.

Mukherjee et al had conducted study of 10 patients having hyperkeratosis and were treated with iontophoretic sodium salicylate in total of 6-8 sittings with excellent results. But in that case series, no any variables or scores were evaluated and there was no any comparison group also.[19]

The present study acts as its own control. The parameters in our study are useful for grading of severity of keratoderma and they can also be used to monitor effect of treatment. Our results are based on the best available scoring systems and are analyzed by appropriate statistics, which were interpreted strictly.

So, salicylic acid is surely an effective keratolytic when used in adequate concentration (i.e., 12%) or with effective modality (iontophoresis). But iontophoresis device has not added any significant impact on treatment outcome when compared to topical.

Limitations

In current study, patients were followed up for only 2 months post treatment to observe any recurrence. Also, we have evaluated response in only plantar keratoderma patients, so efficacy in palmar keratoderma is yet to be established.

CONCLUSION

The present study stated that iontophoresis, although it is efficacious, it doesn't add any additional benefit over topical ointment in management part. The scores and parameters from the study may direct similar future studies. Our results will serve as an authentic reference for future studies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Somani SP, Astik BN, Mehta HH, Jhavar MD. Efficacy and safety of iontophoresis combined sodium salicylate in acquired plantar keratoderma-a randomized controlled study. Int J Res Dermatol 2022;8:101-9.