Original Article

Assessing the Effectiveness of Potent Topical Steroids Alone and Combined with Salicylic Acid or 20% Urea in the Treatment of Mild to Moderate Chronic Plaque Psoriasis: A Randomized Controlled Trial

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Abstract

Background: Chronic plaque psoriasis is a prevalent immune mediated skin disorder marked by the development of thick plaques covered with silvery scales mostly on the extensor surfaces of body. A variety of therapeutic options exist to manage this condition such as corticosteroids, vitamin D analogs, and retinoids, keratolytics and phototherapy. Urea is a strong emollient and keratolytic agent, helpful in reduction of scales in psoriasis. Beneficial effects of topical urea preparations have been shown by various studies but none has assessed its efficacy with betamethasone ointment. This study aimed to fill this research gap.

Objectives: To assess the effectiveness of 20% urea combined with betamethasone vs betamethasone ointment alone or in combination with salicylic acid in the treatment of mild to moderate chronic plaque psoriasis.

Methods: It is Randomized Control Trial. About 180 patients were enrolled in this study and divided into three groups. Group A Patient applied betamethasone dipropionate 0.05% ointment on lesional skin twice a day, Group B applied betamethasone in combination with salicylic acid and patients in Group C applied 20% urea in combination with betamethasone for 6 months regularly. The main outcome was reduction of PASI score from the baseline. Final results were compiled after 6 months keeping p value of <0.05 as significant.

Results: The mean age in Group A, B and C was 31.19 ± 6.87, 29.46 ± and 7.83, 28.83 ± 7.51 years respectively. Duration of disease and male to female ratio was comparable in both groups. The mean PASI score was10.55 ± 1.63± in Group A ,9.76 ± 2.77± in Group B and 9.916 ± 1.78 in Group C. After 6 months it reduced to 10.02 ± 1.79, 8.54 ± 1.92 and 7.66 ± 1.34 in Group A, B & C respectively (p value=.00034).

Conclusion: It is concluded that 20% urea gives better results than salicylic acid when both were combined with betamethasone.

Keywords: Betamethasone Chronic plaque psoriasis, PASI score, Urea.

Received: 24-03-2024 **Revision:** 18-10-2024 **Accepted:** 26-02-2025

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Introduction

Chronic plaque psoriasis, a systemic inflammatory immune-mediated illness, usually have a recurring and remitting pattern. Approximately 80–90% of psoriatic individuals have plaque psoriasis, which is the most prevalent form and is characterized by well-defined, scaly, erythematous plaques that may or may not be itchy and commonly affect areas such extensors of upper and lower limbs, scalp and sacral region.[1] Long-term management techniques are necessary to achieve skin clearance and optimize long-term result due to the chronic nature of the disease and its significant impact on patient quality of life.

Plaque psoriasis severity as determined by body surface area (BSA) and the Psoriasis Area and Severity Index (PASI score) varies among patients but approximately 80% of psoriasis patients have localized, usually mild-to-moderate, disease[2]. The treatment is based on disease severity and topical drugs are the first line of treatment for majority of patients. The aim of treatments is inducing remission and reducing inflammation, scaling, itching, burning, and skin dryness. Currently topical treatments include corticosteroids vitamin D analogs, formulations, vitamin A derivatives (tazarotene), anthralin, Urea, salicylic acid and various formulations of tar. To improve therapeutic outcomes, topical therapies can be administered either alone or in conjunction with systemic treatment as adjuvants.[3]

The first line topical therapy is corticosteroids. Corticoids have a variety of actions, including vasoconstrictive, anti-inflammatory, antimitotic, apoptotic, and immunomodulatory effects.[4] Steroids acts via two important pathways to reduce the inflammatory cascade, namely genomic and nongenomic pathways. Genomic pathway leads to inhibition of new protein synthesis and cytokine production while the faster effects of glucocorticoids, which manifest within minutes, are mediated through non-genomic pathways that consider membrane-bound receptors and second messengers[5]. The maturation, differentiation, and proliferation of immune cells, including dendritic cells (DCs) and macrophages, are frequently inhibited by these two pathways leading to a shift in adaptive immune responses from a T_h1 type to a T_h2 type.[6] All these effects contribute to reduced scaling, pruritus, erythema and induration in psoriasis. Nevertheless, cutaneous atrophy, rebound following treatment cessation, and tachyphylaxis are major side effects of corticosteroids.[7] Therefore, the use of other topicals and adjuvants become necessary for the long-term management of psoriasis.

Salicylic acid is the most commonly keratolytic in psoriasis and other dermatological conditions. By dissolving the intercellular cement material, it decreases intercellular cohesiveness between corneocytes and lowers the pH of the stratum corneum, which increases epidermal hydration and softening.[8] It is most beneficial in extremely thicker scaly psoriatic plaques Topical salicylates also decrease pruritus and, at lower concentrations, they possess antibacterial and antifungal properties. Salicylic acid also promotes permeability of other topical therapies including corticosteroids owing to its keratolytic and penetration-boosting properties leading to improved efficacy.[9] Higher concentrations may lead to local or systemic toxicity ranging from local irritation such as stinging, burning, xerosis, scaling, exfoliation or contact dermatitis to oral pain, headache, dizziness, tinnitus, metabolic acidosis, nausea, vomiting, and hyperventilation.[10]

Topical urea is used for its keratolytic properties, commonly in scaly skin conditions like psoriasis, eczema, calluses, and xerosis. Previously it was employed as a proteolytic agent for wound debridement as well as a topical bacteriostatic agent[11]. Its mechanism of action primarily involves its ability to disrupt the structure of keratin, a major component of stratum corneum, thereby facilitating its removal. Additionally, urea's hygroscopic nature enables it to attract water from deeper skin layers, enhancing skin hydration and promoting smoother, softer skin texture. Urea reduces trans epidermal water loss resulting from urea-induced osmotic stress[12]. Urea is absorbed by a distinct mechanism involving two different urea transporters, which are upregulated by urea itself.[13]

Urea is also involved in gene transcription and epidermal differentiation. Transglutaminase 1, involucrin, filaggrin, and loricrin are among the important genes that are regulated by urea. Each of these gene products contributes to keratinocytes differentiation and the synthesis of antimicrobial peptides. Interestingly alterations in these gene expression have been reported in psoriatic and atopic patients resulting in deranged epidermal DNA synthesis and proliferation.[14,15]

Rationale: Many studies in the past evaluated

the efficacy of topical salicylic acid and other keratolytics in the treatment of mild to moderate chronic plaque psoriasis but there is limited comparative evidence assessing their effectiveness when combined with potent topical steroids in a randomized manner. This study aimed to reduce this research gap.

Methods

It was a randomized controlled trial and a total of 180 patients participated. Sample size was calculated keeping power of the test 80% and confidence interval 95%. Patients were equally randomized into three groups, each consisting of 60 patients. Written consent was obtained and study procedure, and possible adverse effects and complications were explained to them. Basic demographic data was collected and PASI score calculated for each patient. Group A patient used topical Betamethasone dipropionate ointment (0.05%), Group B used combination of Betamethasone (0.05%) and salicylic ointment (3%) while patients in Group C applied Betamethasone dipropionate (0.05%) in combination with urea cream (20%) regularly for 6 months. The frequency of application was twice a day in all groups. For scalp involvement, all patients used Tar shampoo like Megatar, Unitar etc. Patients are called for monthly follow-up and final results calculated at the end of 6 months. Efficacy was assessed based on reduction in PASI score compared to baseline, keeping p value <0.05 as significant. Similarly various adverse effects developed during the study were noted.

The Psoriasis Area and Severity Index (PASI) score is a crucial measurement tool used in dermatology to assess the severity and extent of psoriasis. PASI takes into account the extent of the body affected by psoriasis, as well as the severity of erythema (redness), induration (thickness), and desquamation (scaling). Its score ranges from 0 to 72 with score of <7 considered mild disease,[7-15] moderate, and a score > 15 is considered severe.[16] The current standard for the majority of psoriasis clinical studies is a 75% reduction in the PASI score (PASI 75). This scoring system enables healthcare professionals to objectively evaluate the effectiveness of various treatments and track changes in the condition over time. By quantifying the severity of psoriasis, PASI scores aid in treatment decision-making, allowing for tailored approaches to manage this complex condition and improve patients' quality of life.

The criteria for inclusion in this study that both genders with diagnosed chronic plaque form of psoriasis having mild to moderate severity based on PASI score (<15), between 18-60 years of age and >1 year of disease duration.

The criteria for this study that patients with unstable and other forms of psoriasis (guttate, erythrodermic, exfoliative, or pustular), pregnancy, lactation and others chronic illness, organ transplant patients or using immunosuppressives, HIV infection, or another immunocompromised state. Using biologic therapies in the past six months; systemic steroids/topical steroids, radiotherapy, or other topical antipsoraitic drugs in the past 1 month also led to exclusion from the study.

Results

Statistical analyses were done using SPSS (Statistical Package for Social Science) statistical software (version 22.0). Mean and standard deviation were used for continuous variables like age, disease duration and PASI score. Frequency and percentages were used for nominal variables like gender. For means comparison one way ANOVA was used. Analysis was based on the intention to-treat principle and involved all randomized patients. Data was summarized in the form of tables and charts. Chi square test was used to determine the difference between the groups and a two-sided P-value ≤0.05 was considered statistically significant.

The basic demographic parameters of all patients are shown in Table 1. The mean age & duration of disease in Group A, B and C was 31.19 ± 6.87&7.49 ± 4.40, 29.46 ± 7.83&8.86 ± 5.32 and 28.83 ± 7.51&9.48 ± 4.99 years respectively. Overall male patients were in predominance, 56% in Group A, 68% in Group B and 51% in Group C.

Family history positivity ranged from 8-11%. The mean baseline PASI score was 10.55 ± 1.63 in Group A, 9.76 ± 2.77 in group B and 9.916± 1.78 in Group C (p value >0.05). This was reduced to 10.02 ± 1.79 ,8.54 ± 1.92, and 7.66 ± 1.34 in Group A, B and C respectively (p value =.00034, using ANOVA). Intragroup PASI score difference is shown in Table 2. Changes in PASI score over time are depicted in Figure. 1, showing greater and rapid reduction in PASI score in Group C patients.

Table 1: Showing basic clinical and demographic data of the patients

Parameter	Group A	Group B	Group C	P value
Number of patients	80	80	80	-----
Age (Years)	31.19 ± 6.87	29.46 ± 7.83	28.83 ± 7.51	0.20
Disease Duration (Years)	7.49 ± 4.40	8.86 ± 5.32	9.48 ± 4.99	.079
Gender				
Male	34	41	31	
Female	26	19	29	
Family History	11.8%	10.5%	8.66%	
Baseline PASI score	10.55 ± 1.63	9.76 ± 2.77	9.916± 1.78	.096
PASI score after 6 months	10.02 ± 1.79	8.54 ± 1.92	7.66 ± 1.34	.00034

Table 2: *PASI score difference within the groups.*

Groups	PASI Score		P value
	Baseline	6 Months	
A	10.55	10.02	0.092
B	9.76	8.54	0.0059
C	9.91	7.66	< 0.0001

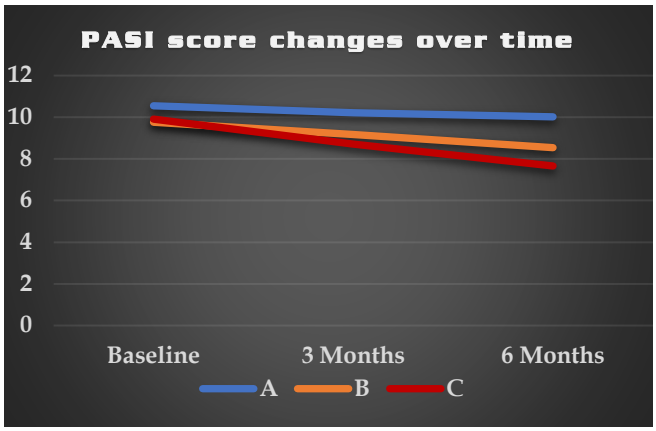

Figure 1: *PASI score at baseline, 3 months and 6 months.*

Discussion

Psoriasis is a chronic inflammatory skin condition having significant physical and psychosocial impact on patient life. Various treatment modalities are available ranging from topical to systemic immunomodulators and biologics. Potent topical steroids are the first line drugs in most cases. Till date no study has compared the efficacy of topical steroids in combination with salicylic acid or 20% urea. In order to fill the research gap, we conducted this randomized control study consisting of 240 patients which showed betters results for 20% urea when combined with betamethasone compared to betamethasone ointment either alone or in combination with salicylic acid in the treatment of plaque psoriasis as assessed by PASI score reduction.

Demographics comparable to our study was shown in a clinical trial conducted by Sidra Khan, et al. Then mean age and duration of disease was 37.85 ± 12.21 & 5.27 ± 3.084 years respectively. There was male predominance with 2% male and 48% female patients. The Mean PASI score was 18.47 ± 8.157, and this high score can be explained by the fact that patients with severe psoriasis having greater PASI score were also included in this study.[17] Many other local and international studies also noted similar demographic data including an Indian study by Farhat Fatema et al.[18]

The therapeutic effectiveness and safety of Betamethasone was assessed by means of PASI, DLQI and c-reactive protein (CRP) in a study by et all conducted in JPMC Karachi. 75 patients with chronic plaque psoriasis applied Betamethasone (0.1%) ointment on lesional areas once daily for 6 months. On final assessment a significant improvement was seen in terms of PASI, DLQI and CRP reduction (p value <0.05). Similarly, only a minor percentage of patient developed local adverse reactions.[19]

A study conducted by Narayana Goruntla et al, compared the efficacy of 6% salicylic acid (Group A) and 0.05% of clobetasol propionate (Group B) ointment in limited plaque psoriasis.

Seventy-five Patients were divided into two groups at random with one group applied salicylic acid while another clobetasol propionate ointment of the lesional skin. Initially the reduction in PASI score was more rapid in Group A but at the end of 3 months, mean PASI score difference between the groups was non-significant (p value=0.21).[20]

A randomized controlled study conducted by Sujay Khandpur assessed the efficacy of salicylic acid in combination with coal in the treatment of limited plaque psoriasis. Among the 62 patients, half patients (Group A) received coal tar (6%) in combination with salicylic acid (3%) while another half (Group B) applied calipotriol/ betamethasone ointment regularly for 3 months. The frequency of application was once at night in both groups. Initially the severity of disease measured by PASI and physician global assessment score decreased rapidly in Group B but after 3 months this difference was non-significant.[21]

Plaque psoriasis was treated with salicylic as sequential therapy in a randomized trial conducted by GS Tiplicaa et al. The study duration was 3 weeks. One group of patients (N=184) used salicylic acid% in combination with mometasone furoate 0.1% for the first week followed by mometasone furoate only for remaining 2 weeks. The second group (176 patients) was treated with mometasone furoate 0.1% for 3 weeks. There was significant reduction in disease severity scores in the first group as assessed by PASI and DLQI. No major adverse effects were noted in patients who received sequential therapy.[22]

In a prospective study by Høvding G et al, scalp psoriasis was treated with combination of salicylic acid (2%) and betamethasone (0.05%) in lotion formulation. For four weeks, eight individuals with varying degrees of severity and duration of scalp psoriasis received treatment. Treatment response was assessed using visual analogue scale. Among all signs and symptoms like Pruritus was first to be reduced followed by signs including scaling, excoriation and induration. 79% of patients were free of scaling after 4 weeks.[23] Similar beneficial effects of salicylic acid combination with steroids are shown by many other studies.[24,25]

The efficacy of topical ureas was studied in a trail by I Hagemann et al. Ten patients were enrolled in the study and psoriasis plaques were treated consecutively for 2 weeks with 10%urea containing ointment ,vehicle alone or left untreated. Efficacy was assessed using clinical score, hydration of the stratum corneum, trans epidermal water loss (TEWL), and immunohistochemical studies. Compared to vehicle alone, Patients in the first group achieved 50% improvement in clinical score, a 29% reduction in epidermal thickness ($p < 0.01$); 51% decreased in epidermal proliferation ($p < 0.005$) and significant increase in epidermal hydration. It's interesting to note that there was a partial reversal of the altered expression of cytokeratins and involucrin (induction of CK 6 and 17 and reduction of CK 5, 1, and 10).[26]

An Italian study evaluated the efficacy of topical steroids in combination with urea and other keratolytics in order to treat plaque psoriasis. Twelve patients applied either HVC (hydrocortisone valerate 0.1% cream) alone twice daily or combination of HCV+EKC (urea 20%, salicylic acid 2% and niacinamide 2% once-daily on symmetrical psoriasis lesions for 4 weeks. The primary and secondary efficacy parameter were reduction in skin thickness assessed by high resolution ultrasound and 5-point Target Lesion score respectively. Results showed equal efficacy of once daily combination regime with the advantage of steroid sparing effects.[27]

As there was no long-term follow-up of patients, therefore disease progression and relapse/remission could not be anticipated in this study. Secondly small sample size was another limitation making generatability of the results difficult. As there are limited number of clinical trials conducted so far on the efficacy of urea in plaque psoriasis, so large centers studies enrolling greater number of patients are needed.

Conclusion

It is concluded that in order to treat mild to moderate plaque psoriasis, topical 20% urea in combination with potent steroids give better results as measure by PASI score reduction, compared to potent steroids alone or in combined with salicylic acid.

Ethical Approval: The study was approved by vide letter No 1231 THQ.

Conflict of Interest: There was no conflict of interest to be declared by any author.

Funding Source: None.

Author's Contribution

HK: Conception and design, acquisition of data, analysis and interpretation, drafting of article, final approval of the version.

MF: Conception and design, analysis and interpretation, drafting of article, critical revision for important intellectual content, final approval of the version

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