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A comparative study to evaluate efficacy & safety of topical monotherapy with tazarotene & calcitriol versus their topical sequential treatment in chronic stable plaque psoriasis

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ABSTRACT

Psoriasis is a chronic and recurring, multi-system inflammatory disease characterised by scaly, painful and disfiguring skin lesions. Stable plaque psoriasis is the most common form, affecting 80-90% of the patients**.** Aim of this study is to compare the safety and efficacy of the Topical sequential therapy with Tazarotene and Calcitriol with their monotherapies in stable plaque psoriasis. Total no. of 120 patients having more than 18 years of age with lesions of more than 3 months was included. 4 groups of pts were given different drug regimen upto 4 & 8 wks. It was concluded that topical treatment with tazarotene and calcitriol are efficacious in the treatment of mild to moderate stable plaque psoriasis as both sequential and monotherapy. Although, topical treatment with calcitriol as monotherapy is far more efficacious and safe than monotherapy and sequential therapy with tazarotene. Also, calcitriol has better patient acceptability than tazarotene.

Key words: Stable Plaque Psoriasis, Topical Treatment, Tazarotene, Calcitriol, Monotherapy, Sequential Therapy

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INTRODUCTION

Psoriasis is a chronic and recurring, multi-system inflammatory disease. Patients with psoriasis often present with scaly, painful and disfiguring skin lesions. Apart from the environmental factors, physical trauma in the form of excessive rubbing or scratching can also stimulate the proliferative process.Other triggering factors include psychological stress, preceding or concurrent streptococcal infection, medications like systemic glucocorticoids, oral lithium, anti-malarial drugs, systemic interferon, beta blockers and angiotensin converting enzyme inhibitors. Psoriasis may also be aggravated by consumption of alcohol and smoking.[1-8]It has also been associated with severe co morbidities such as inflammatory bowel disease, multiple sclerosis, cardiovascular disease, metabolic syndrome and lymphoma**.**[9]

*Stable plaque psoriasis*is the most common form, affecting 80-90% of the patients**.**[11] It is also an important cause of psychosocial morbidity having an adverse impact on the quality of life of patients varying from poor self esteem to suicidal ideation with decreased occupational functionality**.**[12] Stable plaque psoriasis is characterized by well defined thick, red, raised areas with silvery white scales which are loosely adherent. Though these plaques can be found anywhere on the body, they preferentially affect elbows, knees, lumbosacral area, intergluteal cleft and scalp**.**[13] The physical impact of the disease is based on the degree or extent of skin involvement, determined by patient`s affected body surface area (BSA): mild= BSA <3%; moderate=BSA 3-10%; and severe =BSA>10%**.**[14]

Assessment of disease severity

The basic characteristics of the lesions of psoriasis- erythema, induration, and desquamation- provide a means of assessing the severity of psoriasis. Psoriasis causes psychosocial morbidity causing a significant impact on the quality of life of patients. The goals of the therapy are to gain rapid of control of the disease, decrease the BSA involved, decrease the erythema, scaling and induration of individual plaques, and avoid relapse and adverse effects and to improve the quality of life of the patient**.**[15]

The systemic treatment options include phototherapy, cyclosporine, methotrexate, oral retinoids and the newer biologic agents. Due to adverse effects like hepatotoxicity, nephrotoxicity, teratogenecity and malignancy; the systemic therapies are unsuitable for chronic use resulting in cycles of remission and recurrence. Amongst the topical treatments the options are topical steroids, coal tar, vitamin D3 analogues, anthralin, salicylic acid, tazarotene and moisturizers. Though these are not free of adverse effects but are certainly low risk therapies.[16]

The corticosteroids are efficacious and well tolerated and their action is attributed to multiple mechanisms including anti-inflammatory, immunosuppressive and anti proliferative effects.Many authors had shown in their study that the adverse effects of corticosteroids like skin atrophy, striae, pigmentary changes, skin irritation and systemic effects like hypothalamic pituitary axis suppression, adrenal suppression, Cushing syndrome and hyperglycemia can take place.

Tazarotene is a synthetic, acetylenic retinoid which functions via its active metabolite, tazarotenic acid. It is the only topical vitamin A derivative effective for psoriasis and acts on the retinoic acid receptors, suppresses inflammation, inhibits proliferation and causes normalization of cell differentiation in the epidermal layer.

Topical vitamin D3 analogues like calcipotriene (calcipotriol) and calcitriol are safe and effective as both monotherapy and in combination therapy. They act on vitamin D receptors located on T lymphocytes and keratinocytes and inhibit keratinocyte proliferation, promote keratinocyte differentiation, and decrease inflammation in psoriatic lesions. Exposure to sun should be avoided and is indicated for once daily use. It is available as gel and in 0.05% and 0.1% strengths.

Numerous studies[17,18,19] established that the short contact therapy of tazarotene was proven to be well tolerated and equally efficacious as traditionaltherapy, whereas many authours described that vitamin D analogues had been demonstrated to be equally effective as mid potency steroids.

Some researchers[20-25] showed in their study that Calcitriol, a naturally occurring hormonally active metabolite of vitamin D3 shows apparent improvement in 2 weeks and even increased tolerability of Calcitriol in sensitive regions like face, hairline and post auricular and flexural areas, thus allowing better individualization in psoriasis management.

On other hand some showed in their study[26] that topical Calcitriol does not result in systemic hypercalcemia even when applied to one- third of the body surface area or when used continuously over a 52 week time period.

The study on sequential therapy with tazarotene 0.1% and calcitriol 0.0003% has not been tried so far [26,27,28] hence the aim of this study to compare

safety and efficacy of sequential therapy with tazarotene 0.1% and calcitriol 0.0003% vs. monotherapy in stable plaque psoriasis.Intermittent or rotational therapy with frequent alterations in treatment options is usually needed to reduce toxicity of anti-psoriatic drugs in the absence of safer alternatives.[29]

MATERIALS & METHODS

This prospective, randomized, parallel group study was conducted at Santosh Medical College and Hospital and nearby other hospitals in patients suffering from stable plaque psoriasis. After the approval from the Institutional Ethics committee, patients with a diagnosis of stable plaque psoriasis at Santosh Medical College were screened. Patients who fulfilled the following inclusion criteria were enrolled in the study after receiving their written informed consent. This study was undertaken between the duration of Feb 2017 to March 2018. Inclusion criteria comprises patients of both genders, age more than 18 and patients with a clinical diagnosis of stable plaque psoriasis for at least 3 months and subjects with patients with 5 to 10% body surface areainvolvement, whereas exclusion criterias include pregnant females, lactating mother, patients having superficial lesions, clinical diagnosis of unstable forms of psoriasis or associated inflammatory skin diseases, pigmentation, hypercalcemia, vitamin D toxicity and patients who are unresponsive to other topical therapy or within one month prior use of Systemic steroids, Systemic antibiotics, Systemic antipsoriatic treatment, PUVA therapy, UVB therapy, Systemic anti-inflammatory agents andwho were on topical treatment with corticosteroids, immunosuppressive drugs (e.g. tacrolimus, pimecrolimus),retinoids as well as pts using topical products other than the assigned treatment (including moisturizers, new brands of cosmetics ,ointments, lotions and powders)applied on or near the affected area.Pts taking non antipsoriatic concomitant medication that could affect psoriasis (e.g.betablockers, lithium) were excluded from the present study.

METHODOLOGY

Total no. of 150 patients attending the OPD were screened initially and after applying inclusion and exclusion criteria, after obtaining the written informed prior consent of the patient invernacular, and a thorough clinical examination 120 patients coming to OPD between February 2017 to March 2018 were randomized into 4 groups (30 patients in each group) as per random number table.Group A applied Tazarotene 0.1% for 4 weeks followed by Calcitriol 0.0003% for next 4weeks. Group B applied Calcitriol 0.0003% for 4 weeks followed by Tazarotene 0.1% for the next 4weeks.Group C applied Tazarotene 0.1% for 8 weeks.Group D applied Calcitriol 0.0003% for 8 weeks.

Tazarotene was applied as short contact therapy; the patients were instructed to apply the medicine and wash it with water after 20 minutes. Both Tazarotene and Calcitriol were applied once a day in all the 4 groups.

The patients were reviewed at the follow-ups of 4, 8, 12 and 16 weeks. At each visit the patients were assessed clinically and the area of the lesion examined. History regarding any adverse drug reactions and regular drug application was taken. The medications were applied for 8 weeks and then followed up for another 8weeks for remission. During this 8 weeks follow up period, patients were allowed to apply an emollient.
Obtained findings were analysed using appropriate statistical analysis method.

RESULTS AND DISCUSSION

The present study population comprised 120 newly diagnosed cases of chronic stable plaque psoriasis randomly assigned into 4 groups: group A,B,C and D. Patients were evaluated for safety and efficacy during each follow up visit. Efficacy was compared based on the changes in erythema, scaling, plaque elevation and patient`s assessment score. Number of adverse events reported at each visit was noted to compare safety.

Pretreatment composition of study groups: This study was done to compare the safety and efficacy of topical sequential treatment with Tazarotene and Calcitriol vs. monotherapy in stable plaque psoriasis showed the following results. Primary outcome measures include Mean difference in Erythema, Scaling, Induration, patient`s own assessment of diseaseseverity, whereas secondary outcome measures include Period of remission & No. of adverse eventsreported.

Demographic profile of the patients is given in Table 1. The mean age of the patients was comparable in the four groups (39.47±11.83 years in Group A, 36.83±11.25 years in Group B, 35.53±12.76 years in Group C and 33.33±15.01 years in Group D). Out of total 120 patients, 58 were males and 62 females making a male-female distribution of 48% and52%.

Clinical profile of the patients is given in Table 2. The mean duration of illness was also comparable in the four groups (4.35±3.19 years in Group A, 5.19±4.22 years in Group B, 5.9±4.80 years in Group C and 4.75±4.14 years in Group D). The pretreatment scores of erythema, scaling and

plaque elevation were also comparable among the four groups and no significant difference was noted. Evaluation of efficacy was represented in different tables each group.

Discussion

There were 58 males and 62 females in our study and the overall sex ratio in our study was 0.93:1. (Table 1) In the general population, both males and females are said to be equally affected by psoriasis, and there is also no evidence that the disease is phenotypically different in the 2 sexes.[41]Our study also demonstrated equal distribution of the disease among both the sexes, which is presented in table 1.

The mean duration of illness was 4.35±3.19 years in Group A, 5.19±4.22 years in Group B, 5.9±4.80 years in Group C and 4.75±4.14 years in Group D. The difference in the duration of illness in the four groups was not statistically significant. The overall mean duration of illness was 5.05±4.12 years.(Table 1 & 2) These findings are in accordancetothe study performed by Lahfaet al[37], the mean duration of illness among the patient group receiving calcitriol was 16 years, which was much higher than seen in the present study. However, Mehta et al[35]had established that the patient group receiving tazarotene the mean duration of illness was 2.46 years. Our findings also find a place within the range of the two studies.

While assessing the response to treatment comparison between 4 groups demonstrated a significant decrease in the scores of erythema, scaling, plaque elevation and patient`s assessment score in Group Di.e patients on treatment with calcitriol which is illustrated in table 6. The results of present study are comparable to the results of studies done previously on topical calcitriol. Lahfaet al[37] observed that successful clinical response at endpoint as revealed by global assessment by investigators was seen in majority of patients treated with topical calcitriol. Similarly, Barker et al[38] found global severity scores for psoriasis showed marked improvement from baseline to end of treatment phase with topical calcitriol. Various other studies done by Wishartet al[41]and Saggese et al[42] have also demonstrated the efficacy of topical calcitriol for short term treatment of patients. Our study also demonstrated better response to treatment as per patient assessment. This finding is also consistent with the observation made by Ortonne et al[36] in their study. In their study, subjects considered efficacy to be greater on the calcitriol treated lesions and also showed subject`s global preference in favour of calcitriol with 57% of the subjects rating calcitriol as being better.

Our study showed that topical calcitriolie group D (Table 6) had significant improvement in all four parameters i.e erythema, scaling, induration and patient assessment as compared to tazarotenei.e group C. A study performed by by TZung et al[43] comparing tazarotene 0.1% gel plus petrolatum with calcipotriol 0.005 % inferred better treatment success rates as assess by patients themselves with calcipotriol treated side had shown the comparable result. He established that 85% patients reported treatment success with calcipotriol as compared to 74 % with tazarotene. A similar right-left side intra individual 8 week parallel study done to directly compare calcipotriol and tazarotene was conducted by Kaur et al[28] on 17 patients. The study inferred that calcipotriol treated lesions produced moderate to marked improvement as compared to tazarotene 0.05% at both 4 and 8 weeks. Although this study also revealed comparable improvement calcipotriol and tazarotene 0.1% at the end of 4 and 8 weeks, findings of our study are consistent with the earlier study.

Present study demonstrated a reduction in the erythema score from baseline to the subsequent follow upvisits whereas table 3 depict a decrease in the scaling score of group A. Table 3 exhibits a reduction in the plaque elevation score from baseline to subsequent visit, while table 3 illustrate the changes in the patient assessment score from baseline to the end of 16weeks of group A.Table 4 depict the decrease in erythema score from 0 weeks to subsequent follow up visits as well as table 4 display the decrease in the mean scaling score of group B, while table 4 demonstrate the change in the plaque elevation score during the study period. Table 4 portray the changes in the patient`s assessment score of group B.

It was observed that significant improvement in patients in group A and B i.e on sequential therapy. Tanghetti EA et al.[27]had proved that substantial additional improvement in efficacy and patient satisfaction was observed in patients switched from topical vitamin D analog to tazarotene. While patients of Group A and B on sequential therapy in our study did not show statistically significant difference when comparison done between four groups.

Assessment of side effects were observed in 18 /120 (15%) of the all patients. Gerritsenet al[44]had demonstrated that topical calcitriol is safe even on long term use. Similar results were noted by Langneret al[39] in their study on long term use of calcitriol. Ortonneet al.[36]also showed in their right –left comparison study that calcitriol was better tolerated and perilesional erythema and burning was significantly less severe with calcitriol. Whereas Zhu et al[45] lower cutaneous discomfort

and better patient acceptance was observed with calcitriol. Present study also demonstrated similar results though only 1 patient reporting mild itching and one complaining of irritation which noted during the initial phase and subsided with continued treatment.

Out of 18 patients reporting side effects 12 were treated with tazarotene group. Mehta et al[35] had revealed higher incidence of side effects were noticed with tazarotene, 6 out of 17 reported itching and 4 patients reported irritation. Present study stated fewer incidences of side effects with tazarotene which can be justified by the fact that short contact therapy for tazarotene was used. Study done by Veraldi et al [19] supported that tazarotene used as short contact therapy is better tolerated than the traditional treatment with tazarotene.

Our study also reported similar results with short contact therapy. Lower rate of irritation and better tolerability has been documented by Koo et al[12] for the formulation of tazarotene. Since the patients in our study were also treated with tazarotene, that is another reason for lesser incidence of side effects with tazarotene. Though no patient reported increase in erythema in the study done by Mehta et al.[35],4 patients in our study reported increase in erythema which lasted as long as the treatment continued i.e. 8 weeks.

CONCLUSION

The present study was conducted at Santosh Medical College and Hospital and nearby other hospitals on 120 patients newly diagnosed case suffering with chronic stable plaque psoriasis attending the OPD at Santosh Medical College & Hospital. 150 patients were screened initially and 120 patients were selected after applying inclusion and exclusion criteria, from February 2017 to March 2018. They were randomly distributed in four groups, 30 patients in each group (Group – A, B, C & D). Patients were evaluated during each follow up visit. Efficacy was compared based on the changes in erythema, scaling, plaque elevation and patient`s assessment score. Number of adverse events reported at each visit was noted to compare safety.

Significant clinical improvement was observed in all the four groups as compared to baseline. However, intergroup analysis revealed better results in calcitriol group.

The side effects noticed were itching, burning and skin irritation. However few patients reported mild side effects of the medications but no patient discontinued the treatment because of the side effects.

It was concluded that topical treatment with tazarotene 0.1% and calcitriol 0.003% are efficacious in the treatment of mild to moderate stable plaque psoriasis as both sequential and monotherapy. However, topical treatment with calcitriol as monotherapy is far more efficacious and safer than monotherapy and sequential therapy with tazarotene. Also, calcitriol has better patient acceptability thantazarotene.

Both calcitriol and tazarotene are newer topical treatment modalities in use since a decade in stable plaque psoriasis. Though there are studies comparing their effectiveness in psoriasis with other conventional topical treatments (like coal tar, topical steroids, anthralin). Studies directly comparing calcitriol and tazarotene were not available. Hence, the present study was planned to compare the safety and efficacy of topical sequential treatment with tazarotene and calcitriol vs monotherapy in stable plaque psoriasis.

It was established that topical tazarotene was efficacious as monotherapy as well as sequential therapy in the treatment of mild to moderate psoriasis, while calcitriol as monotherapy was superior in terms of both efficacy and safety.

Table 1. Demographic profile of the patients:

Characteristics	Group A	Group B	Group C	Group D
Age (years)	39.47±11.83	36.83±11.25	35.53±12.76	33.33±15.01
Duration of illness (years)	4.35±3.19	5.19±4.22	5.9±4.80	4.75±4.14
Sex ratio	0.58:1	1.72:1	0.87:1	0.87:1

Table 2. Clinical profile of the patients in 4 Groups

Prior to commencement of treatment	**Group A**	**Group B**	**Group C**	**Group D**
Erythema	3.73±0.78	3.6±0.67	3.5±0.73	3.33±0.92
Scaling	3.37±0.72	3.4±0.62	3.33±1.03	3.3±1.02
Plaque elevation	2.97±0.61	3.2±0.61	2.3±0.53	2.57±0.73
Patient`s own assessment	3.6±0.89	3.7±0.60	4±0.74	3.87±0.78

Table 3. Mean change in Erythema, Scaling, Plaque elevation and Patient's own assessment in Group A.

Weeks	**Erythema**	**Scaling**	**Plaque elevation**	**Patient`s own assessment**
0	3.73±0.78	3.37±0.72	2.97±0.61	3.60±0.89
4	3.47±0.90*	2.43±0.68*	2.00±0.69*	2.60±0.81*
8	2.57±1.10*$^{\#}$	1.67±0.96*$^{\#}$	1.30±0.95*$^{\#}$	2.13±0.97*
12	2.6±1.04*$^{\#}$	1.90±0.88*$^{\#}$	1.47±0.86*$^{\#}$	2.47±0.82*
16	2.93±0.87*$^{\#}$	2.13±0.68*$^{\times}$	1.93±0.64*$^{\times}$	2.80±0.76*$^{\times}$

Table 4. Mean change in erythema,scaling,plaque elevation and patient`s own assessment in Group B.

Weeks	**Erythema**	**Scaling**	**Plaque elevation**	**Patient`s assessment**
0	3.60±0.67	3.40±0.62	3.20±0.61	3.70±0.60
4	2.57±0.82*	2.47±0.86*	2.20±0.61*	2.67±0.76*
8	2.60±1.04*	1.87±1.14*$^{\#}$	1.47±0.73*$^{\#}$	2.13±1.04*$^{\#}$
12	2.43±0.94*	2.13±0.97*	1.80±0.66*$^{\#}$	2.50±0.94*
16	3.03±0.67*$^{\#}$	2.50±0.90*$^{\times}$	2.07±0.52*$^{\times}$	2.83±0.87*$^{\times}$

Table 5. Mean change in Erythema, Scaling, Plaque elevation & Patient`s own assessment in Group C.

Weeks	Erythema	Scaling	Plaque elevation	Patient's own assessment
0	3.50±0.73	3.33±1.03	2.30±0.53	4±0.74
4	3.20±0.71*	2.73±1.11*	1.80±0.81*	3.27±0.78*
8	3.27±0.87	2.20±1.21*	1.47±0.94*	3.20±0.96*
12	3.13±0.86*	2.37±1.19*	1.70±0.75*	3.48±0.83*
16	3.43±0.77	2.63±1.07*	1.93±0.64*$^{\times}$	4.07±0.64*$^{\#\times}$

Table 6. Mean change in erythema, scaling, plaque elevation and patient`s own assessment in Group D.

Weeks	Erythema	Scaling	Plaque elevation	Patient`s own assessment
0	3.33±0.92	3.30±1.02	2.57±0.73	3.87±0.78
4	2.53±0.82*	2.47±1.17*	2.10±0.84*	2.93±0.83*
8	2.00±0.87*#	1.83±1.29*	1.43±1.17*#	2.23±0.82*#
12	2.17±0.87*	1.80±1.30*#	1.53±1.17*#	2.30±0.92*#
16	2.60±0.93*×	2.23±1.10*	1.87±1.01*	3.13±1.01*×

Table 7. Adverse drug reactions in Group A

Adverse drug reaction	4 weeks	8 weeks	12 weeks	16 weeks
Itching	1	0	0	0
Burning	2	0	0	0
Irritation	0	0	0	0
Increase in erythema	0	0	0	0

Table 8. Adverse drug reactions in Group B

Adverse drug reaction	4 weeks	8 weeks	12 weeks	16 weeks
Itching	0	0	0	0
Burning	0	0	0	0
Irritation	1	0	0	0
Increase in erythema	0	0	0	0

Table 9. Adverse drug reactions in Group C

Adverse drug reaction	4 weeks	8 weeks	12 weeks	16 weeks
Itching	3	1	0	0
Burning	2	1	0	0
Irritation	3	0	0	0
Increase in erythema	4	4	0	0

Table 10. Adverse drug reactions in Group D

Adverse drug reaction	4 weeks	8 weeks	12 weeks	16 weeks
Itching	1	0	0	0
Burning	0	0	0	0
Irritation	1	0	0	0
Increase in erythema	0	0	0	0

Table 11. Studies showing age incidence in psoriasis

Study		Age range (years)	Mean age (years)
Studies evaluating calcitriol	Ortonne et al[36]	18-70	44.5±14.5
	Lahfa et al[37]	Not available	50±14
	Barker et al[90]	19-68	42.43±12.86
	Langner et al[39]	Not available	42.1±12.9
Study evaluating tazarotene	Mehta et al[35]	Not available	35.82
Present study		18-72	36.29±12.82 years.

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