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Comparative Study Of Efficacy and Safety of Topical Active Fragment of Basic Fibroblast Growth Factor (B FGF) 0.1% Solution V/S Betamethasone Valerate 0.1% Ointment in the Treatment of Vitiligo Patients

Dr. P. Kamala Subhashini[1], Dr. K. Sankar[2], Dr. Chandrakala Kambar[3], Dr.V.VenkataRamana[4]

[1]*Assistant Professor, Department of Pharmacology, Siddhartha Medical College, Vijayawada, India.*
[2] *Professor, Department of Pharmacology, Siddhartha Medical College, Vijayawada, India.*
[3]*Associate Professor, Department of Pharmacology, Siddhartha Medical College, Vijayawada, India.*
[4]*Professor and Head, Department of Pharmacology, Siddhartha Medical College, Vijayawada, India.*

Abstract: *Vitiligo is a common acquired pigmentary disorder affecting the skin of all ages and both sexes around the world. Presents as localised milky white patches of depigmentation which tend to progress in due course. It affects about 1% of the world population and the incidence is higher in India ranging from 3% to 8% approximately. There is psychological morbidity due to cosmetic disfigurement and no definite treatment is available. So there is a need to find better drug. The aim of our study is to compare the efficacy and safety of a new drug, Basic fibroblast growth factor {b FGF} 0.1% solution with the standard Betamethasone valerate (BV)0.1% ointment in patients with clinically diagnosed vitiligo. A prospective, comparative and interventional study was done on 62 patients with vitiligo patches, 31 in Group A were put on topical Basic fibroblast growth factor (b FGF) 0.1% solution and 31 in Group B on topical (BV) 0.1% ointment for 16 weeks. At the end of 1st, 2nd,3rd and 4th month the lesions were assessed for repigmentation, appearance of new lesions and adverse effects. After 16 weeks statistical analysis was done with Student T test. Patients in Group A showed more repigmentation in the patches than Group B patients. Topical (b FGF) was found to be more efficacious, safe and tolerable without any major side effects than topical (BV) 0.1% ointment.*

Keywords*: Basic fibroblast growth factor {b FGF}. Betamethasone valerate 0.1% ointment. Vitiligo. White depigmented patches.*

I. Introduction

Vitiligo is a common, acquired recalcitrant disorder characterised by areas of depigmentation resulting from loss of melanocytes in the epidermis. It affects 1% of the world population irrespective of skin colour or ethnic origin, and approximately 3% to 8% of the Indian population. It affects all ages and both sexes. The depigmented patches affect the patient cosmetically and psychologically. The exact aetiology of vitiligo is unknown, but four main theories exist to explain it - the autoimmune hypothesis, the neural hypothesis, the self-destruction hypothesis, and the growth factor defect hypothesis. The typical lesion is circumscribed milky white macule, round to oval in shape, measuring several millimetres to many centimetres, often associated with leucotrichia. It may involve any site of the skin and mucosa but mostly involves wrists, axillae, groins, lower back, loins, palms, soles, finger tips and the scalp. Periorbicular, circumoral, anogenital areas, and glans penis, prepuce and vulva also involved. It is difficult to treat vitiligo though various treatment options available. The standard treatments available are various native medicines, psoralens with phototherapy, topical and systemic corticosteroids, Tacrolimus, placental extract; cosmetic camouflaging and various others are tried with hope. Surgical treatments are also available are tattooing and skin grafting.[1]

1. Active fragment of basic Fibroblast Growth Factor: Is a pleotropic growth factor for variety of cells including melanocytes. In the skin it is secreted by the keratinocytes which are in physical contact with the melanocytes in the epidermis. This keratinocyte-derived bFGF is a natural growth factor for normal human melanocytes in vivo, and also increases melanogenesis. It causes the migration of the melanocytes. After irradiation with ultraviolet B or sunlight its levels increase. It acts during G1 phase and promotes cell cycle progression through the G1/S phase transition. Thus it acts as a mitogen, chemotactic, and chemokinetic agent to the melanocytes.[2]

It has been found that melanocytes in lesions from vitiligo patients showed 'defective growth and passage capacities.' bFGF is inhibited by neutralizing antibodies to it and also by a synthetic peptide that blocks the binding of bFGF to its receptor. bFGF levels were found to be lower in the skin involved than in the non-involved skin of vitiligo patients. Previous studies demonstrated that the basic fibroblast growth factor (bFGF) elaborated by keratinocytes in vitro sustains melanocyte growth and survival. Thus, melanocytes which proliferate at the margins of the vitiligo patch may migrate and populate the patch. It acts as a stimulator of melanin biosynthesis by the melanocytes which proliferate in response to bFGF.

Thus causes repigmentation of the lesion and the progression of repigmentation is also faster. Exposure to sunlight or UV-B rays increases bFGF levels and also the repigmentation in the lesion. bFGF was tried topically over the lesion with achievement of visible repigmentation with almost nil side-effects.[3]

2. Betamethasone valerate: It is a potent topical corticosteroid having anti-inflammatory, antipruritic and vasoconstrictive actions. It causes repigmentation at a slower pace which can be hastened with exposure to sunlight. Many side-effects are seen when used in high doses for a long period, under occlusive dressing. With topical use dryness, itching, burning, local irritation, telangiectasia, striae, atrophy of skin, hypertrichosis, change in pigmentation, secondary infection, acne form eruptions and allergic dermatitis may occur. Topical use can give rise to systemic side- effects like diabetes, osteoporosis, muscle wasting, Cushing's syndrome, growth suppression in children and HPA axis suppression.[1,2]

Keeping the above view in mind, a prospective and comparative study was carried out in clinically diagnosed vitiligo patients to compare the efficacy, safety, compliance and cost effectiveness of Active fragment of basic Fibroblast Growth Factor v/s Betamethasone valerate**.**

II. Aim And Objectives

1. Aim: To compare the efficacy and safety of topical active fragment of basic Fibroblast Growth Factor (bFGF) 0.1% solution v/s Betamethasone valerate 0.1% ointment in the treatment of vitiligo.

2. Objectives:

2.1. To compare the area of regimentation between the two groups.
2.2. To study the adverse effects of the drug in both the groups.
2.3. To compare the compliance of the patients in both the groups.
2.4. To compare the cost effectiveness in both the groups.
2.5. To compare appearance of new lesions in both the group.

III. Materials And Methods

This is a prospective, comparative and interventional study. Patients clinically diagnosed as vitiligo, who attended the Dermatology outpatient department at Government general hospital, Vijayawada, Andhra Pradesh, India.The study was approved by the institutional ethics committee and an informed consent in the local language was taken from every patient. A total number of 65 patients were selected and randomly assigned in two groups.

Group A: 31 patients were included and given active fragment of basic Fibroblast Growth Factor (bFGF) 0.1% solution for topical use.
Group B: 31 patients were given Betamethasone valerate. 0.1% ointment for topical use.

Inclusion criteria: Case of vitiligo involving the face, trunk, limbs with or without mucosal involvement, in the age of 12 to 60 years and both sexes were included. Patients who have not receive any treatment in the last 3 months. Exclusion criteria: Evidence of spontaneous regimentation in any of the lesions, lip/tip vitiligo, Pregnancy/ lactation, and associated co-morbidities like serious cardiovascular/cerebral/renal/hepatic diseases.

1. Method of study: Group A patients were given active fragment of basic Fibroblast Growth Factor 0.1% solution for topical application. Originally (bFGF) is extracted and purified from human placental extracts. It is a solid white lyophilised powder stored at -20 centigrade. The vehicle used to dissolve is made up of 3 different non-polar solvents which have the property of transporting the decapeptide into the epidermis and binding to heparin sulphate on the extracellular matrix and is retained in the epidermis. In the vehicle it is stable at 25 degrees Celsius. As the vehicle is volatile at that temperature, it is kept in the tray under the freezer at 0-4 degrees Celsius but should not be frozen. 20 micro litters with a micropipette over the spot size of 2+2 cm^2 in the evening between 6-7 pm, followed in the morning with exposure to sunlight for 5-10 minutes between 11 am to 3 pm daily.[3] The product bFGF (Melgain) is provided by Issar Pharmaceuticals

Pvt, Ltd. for all the patients in groupA throughout the study period. Group B patients were given Betamethasone valerate 0.1% ointment for topical use in the nights and exposure to sunlight for 10-15 minutes between 11 am and 3 pm daily. Product is Betnovate ointment of Glaxo Company, India.
Initially when the patient was enrolled routine investigations were done.

Measurement of the lesion (cm) with an initial photograph was taken. Later each patient in the two groups were evaluated at the end of 1^{st}, 2^{nd}, 3^{rd} and 4^{th} month for
1.1 Routine investigations.
1.2. Percentage of repigmentation in the patch.
1.3. To watch for adverse effects: itching, erythema, and blistering of the area.
1.4. Planimetry(cm)
1.5. Photographs.

The patients were asked to report any unusual or unpleasant symptoms during the study period. This report included a detailed description of the signs and symptoms of the event, time of onset and duration, whether treatment was discontinued, corrective measures taken, outcome, and other possible causes. Compliance with study medication was determined by regular turning up for the follow ups and drugs vials and ointment tubes.

2. Statistical Analysis: Data obtained was tabulated, statistical analysis was done in Microsoft excel sheet and results were noted in Mean, Standard deviation, Student's t-test and P value was derived.

IV. Results

The study was conducted on 62 cases of stable vitiligo vulgaris. The study started in the month of January 2008 and completed in July 2008. Each patient in both the groups completed a follow up 16 weeks. 3 patients were dropouts in the initial period of the study. All the 62 patients enrolled, were regular for follow up study. each patient in the two groups were evaluated at the end of 1^{st}, 2^{nd}, 3^{rd} and 4^{th} month for routine investigations, the patch was measured in centimetres and percentage of repigmentation in the patch was calculated. Serial photographs of the patch under study were taken. The lesion was observed for any erythema, blistering or tanning of the surrounding skin. Patient was questioned for any complaint of itching or other complaints. Data obtained was tabulated, statistical analysis was done in Microsoft excel sheet and results were noted in Mean, Standard deviation, Student's t-test and P value was derived.

Table No 1: Demographic Data

S.no	Variables	bFGF n (%)	BV n (%)
1.	Sex of the patient Female Male	 12 (39%) 19 (61%)	 17 (55%) 14 (45%)
2.	Age of the patient(yrs) 12 -21 22 -31 32 -41 41 -52 >52	 18 (58%) 3 (10%) 3 (10%) 4 (12%) 3 (10%)	 16 (52%) 5 (16%) 4 (12%) 3 (10%) 3 (10%)
3.	Duration of the disease < 1 year > 1 year	 38 (61%) 24 (39%)	 38 (61%) 24 (39%)
4.	Family history of the disease Present Absent	 9 (29%) 22 (71%)	 10 (30%) 21 (70%)
5.	Type of the lesion Focal Segmental Vulgaris	 12 (39%) 9 (29%) 10 (32%)	 13 (42%) 5 (16%) 13 (42%)
6.	Site of the lesion Head/neck Body Extremities	 14 (45%) 4 (13%) 13 (42%)	 12 (39%) 3 (10%) 16 (51%0
7.	No.of lesion 2 or < 2 >2	 22 (77%) 9 (29%)	 23 (74%) 8 (26%)

Maximum number of patients i.e; 55% (n=34) of the entire study population were 12-21 yrs. In bFGF group, 61% (n =19) male patients, 39% (n=12) female patients were enrolled in the study. In Betamethasone group 55% (n=17) male patients, 45% (n=14) female patients were enrolled in the study. Over all, in both the groups 58% (n=36) male patients, 45% (n=26) female patients were enrolled in the study.

By duration of the disease in both the groups, 61% (n=38) of the patients were enrolled with less than one year of duration of the disease, 39% (n=24), were enrolled with more than one year of duration of the disease. In bFGF group, 29%(n =9) patients had family history of the disease. In Betamethasone group, 32% (n=10) patients had family history of the disease. Overall, 30% (n=19) patients had family history of the disease and 70% (n=43) patients had no family history of the disease in the entire study population.

By the type of lesion, 40% (n=25) of the patients with focal lesions, 23% (n=14) of the patients with segmental lesions, 37% (n=23) of the patients with vitiligo vulgaris lesions were enrolled into the study.

In the entire study population, 42% (n=26) lesions were distributed over head and neck, 11°/0 (n=7) lesions were distributed over body, and 47% (n=29) lesions were distributed over extremities like hands and feet. 72% (n=45) of the study population had 2 or < 2 lesions, and 27% (n=17) had > 2 lesions.

Table No.2 Percentage of response in both the groups

% of repigmentation	bFGF	Betamethasone
>75% or complete	14	0
50 -75%	11	2
< 50%	6	4
No response	0	25

It was observed that 45% (n=14) of the patients who were treated with bFGF, showed more than 75% repigmentation, 35% (n=11) of the patients showed 50 - 75% repigmentation, and 20% (n=6) developed less than 50% repigmentation. Whereas in patients who were treated with Betamethasone, 7% (n=2) showed 50-75% of repigmentation, 13% (n=4) showed less than 50% repigmentation, and 80% (n=25) showed no response at all..

The results are statistically significant" value at df 60, "p"<0.05 after student t test (unpaired, two tailed). Student t test = 1.99. At df = 60, "p" < 0.05, hence the difference of response between the two treatment groups is statistically significant.

13% (n=4) patients experienced local adverse reactions like mild itching, who were treated with bFGF, whereas no patient complained about any adverse reactions in the betamethasone group. In bFGF group 51% (n=16) showed tanning of normal skin, whereas no such change was seen in patients treated with

Betamethasone. In both the groups, no systemic adverse effects were reported or observed. All the laboratory investigations were found to be normal before, during and after the study period.. At the time of final evaluation no new depigmented areas developed in the entire study population. The compliance in the both groups was good as the administration of both drugs was easy and simple.

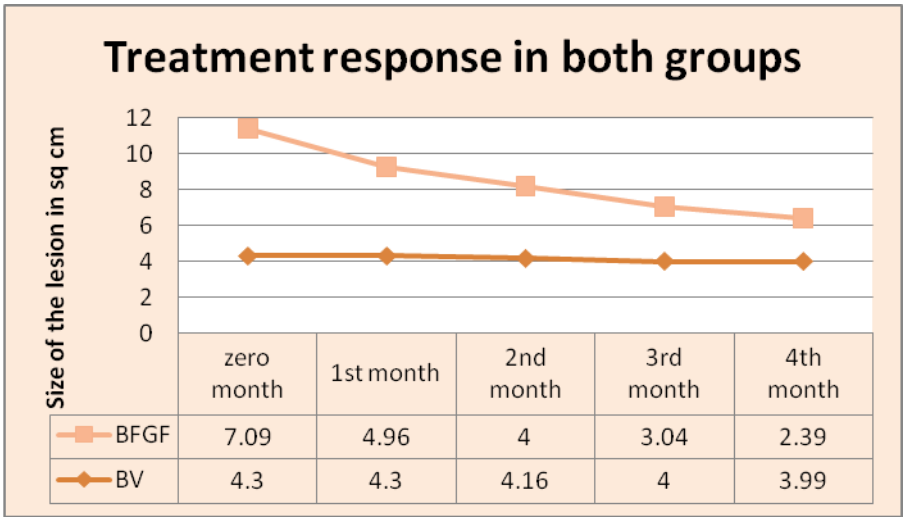

fig no. 1: graph depicting the course of response to treatment in both groups

Cost effectiveness: Cost of 1 roll-on vial of bFGF (Melgain) is Rs. 350. Patients needed 1-2 vials per month. The total cost for 4 month follow up was Rs.1500- 3000. Betamethasone valerate ointment (Betnovate), was Rs. 20 per tube. Patients need 1-2 tubes per month. The total cost for 4 months was Rs. 80-160.

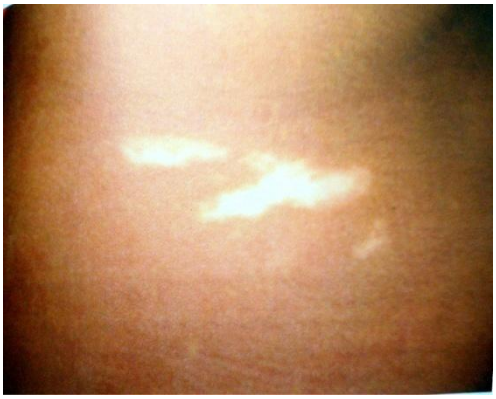

Fig no.2: Before bFGF treatment

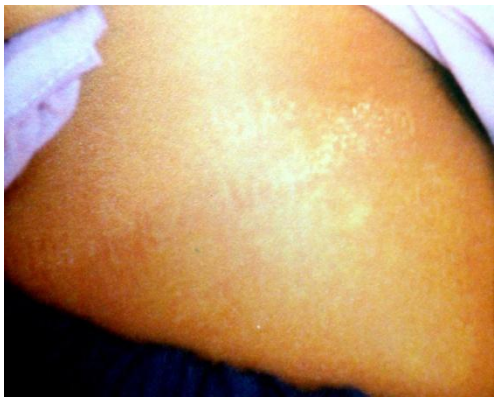

Fig no .3: After bFGF treatment

V. Discussion And Conclusion

Vitiligo is a common acquired depigmentary disorder afflicting people of all ages around the world. There is great concern as the incidence is higher in India ranging from 3% to 8% approximately. Vitiligo is a common skin disorder known from age old periods with many treatment options. The main concern to the patient is cosmetic disfigurement and to the doctor it is the frustration due to high percentage of treatment failure. Patients do not respond to the same treatment in the same expected way. Many modalities of treatments are available, all of them being cumbersome, tedious, expensive and are associated with various adverse effects. Thus treatments fail after long periods of hopeful trying, thus adding to the psychological burden of the patient. Therefore in the quest for simple, safe, efficacious, and cost effective option, basic Fibroblast Growth Factor was studied. This new investigative drug had promising results with minimal adverse effects. A prospective, comparative and interventional study was done with standard drug Betamethasone valerate, in the treatment of vitiligo.

In healthy skin, there is a molecular microenvironment that favours the survival of melanocytes and regulates their function. Keratinocytes synthesize and secrete several cytokines that have stimulatory and inhibitory effects on melanocytes. There is growing evidence that cytokines are important in the depigmentation process of vitiligo. Granulocyte macrophage colony-stimulating factor (GM-CSF), endothelins, b-FGF are the mitogens for melanocytes whereas TNFα, IL1α, IL-6, TGFβ are the potent

inhibitors of melanocyte growth. Studies showed that in the hypo pigmented disorder e.g.: vitiligo, there were changes in their cutaneous microenvironment with increased TNF-α and decreased bFGF mRNA expression. This cytokine microenvironment change may be implicated in the pigment loss and hence these cytokines may have future therapeutic implications.[4,5] Studies also showed lower levels of bFGF in both the involved and the noninvolved skin of vitiligo patients in comparison with the controls.This might highlight the role of bFGF in the pathogenesis of vitiligo[6]. Melanocyte migration is an important event in re-pigmentation of vitiligo. In previous studies it was demonstrated that narrow-band ultraviolet B (UVB) irradiation stimulated cultured keratinocytes to release a significant amount of basic fibroblast growth factor (bFGF). Furthermore, narrow-band UVB enhanced migration of melanocytes. Another study showed significantly enhanced by narrow-band UVB-irradiated keratinocyte supernatants. In these supernatants, a significant increase in basic fibroblast growth factor (bFGF) was found.[7] These results provide a theoretical basis for the effectiveness of narrow-band UVB irradiation in treating vitiligo by increasing bFG[8,9]. It has been suggested that, in vivo, besides direct stimulation, ultraviolet B light stimulates melanocytes indirectly through neighbouring irradiated keratinocytes by an increased bFGF production. Melanocytes could be exposed to bFGF through direct contact with keratinocytes and through the extracellular matrix deposited by neighbouring keratinocytes.

In view of the above clinical studies were conducted to establish the efficacy and safety of bFGF in vitiligo patients. Ramaiah et al in his study with combined bFGF and NB-UVB observed faster results than NB-UVB alone and the side effects of NB-UVB were reduced. In another study he compared with oral mini pulse of betamethasone.[10] A.S.Kumar et al in his comparative study proved better and faster results with bFGF than with steroids, in vitiligo patients. The Issar Pharmaceuticals Pvt, Ltd. conducted many clinical trials and animal model studies with bFGF, to establish its safety and efficacy before marketing the product as Melgain. In view of the above facts, a prospective, comparative and interventional study with bFGF and standard drug Betamethasone valerate was done in the patients of vitiligo. Efficacy and safety profiles of both were compared. Time factor and cost effectiveness were also considered.

At the end of 4 months of study period almost all the patients showed varying degrees of repigmentation in both the groups. The time taken for 75% of repigmentation was less with groupA patients when compared with groupB patients. Total repigmentation with betamethasone took comparatively longer period which may lead to a risk of various local and systemic side effects. Side effects, both local and systemic were negligible in both groups.

The percentage of repigmentation is comparatively more and the time needed for achieving this is also lesser. Mild local side-effects and absence of long term systemic effects gives bFGF an advantage. Patient compliance is also good as it was single application with simple applicator.

The pharmacoeconomic analysis shows that the total cost of bFGF required for complete repigmentation was high. On the other hand Betamethasone is cheaper but longer period of treatment was required for complete repigmentation. Thus finally bFGF is cost effective as its results were reached in shorter time.

From the foregoing, it is obvious that bFGF has a place in therapy of management of vitiligo in following ways:

1. Patient with small patches of vitiligo, especially those on cosmetically important areas can to be treated with bFGF with definitive results.
2. In paediatric age group, where high risk alternatives such as PUV-A / PUVASOL with UVA, and steroids should be avoided, and then bFGF can be tried.
3. As an adjuvant therapy with steroids and PUVA with UVB to avoid long term potential effects of both.
4. bFGF offers a safe, effective and economical option for the future management of vitiligo patients. It is a preliminary study and requires further confirmation by multi-centric clinical evaluation.

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