Evaluation of the Efficacy and Safety of “Hair Loss Cream" in the Management of Telogen Effluvium

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ABSTRACT

Telogen effluvium is a common cause of hair loss, which affects men and women of all ages. Various available therapies have low success rate and are associated with numerous adverse effects, which limit their clinical use. This study was planned to evaluate the efficacy and safety of “Hair Loss Cream (PCPB Hair Cream)” in the management of telogen effluvium. This study was an open, phase III clinical trial, conducted in compliance with the GCP guidelines. One hundred patients of both sexes, suffering from telogen effluvium were enrolled in the study. Patients on immunosuppressive drugs, patients applying any topical therapy in the last 2 weeks prior to the initiation of the study, patients with evidence of skin infection, and pregnant and lactating women were excluded from the study. All the enrolled patients underwent a thorough scalp skin examination and other laboratory investigations. All the patients were advised to apply “Hair Loss Cream (PCPB Hair Cream)” to the scalp, daily at night, for 6 months, and were advised to leave the cream overnight. Patients were told to restrict themselves to “Hair Loss Cream (PCPB Hair Cream)” as the only treatment. All the patients were followed up every month for a period of 6 months. The predefined primary efficacy endpoints were subjective and objective improvements. The predefined secondary safety endpoints were incidence of adverse events and overall patient compliance to the therapy. This study observed a significant reduction in the associated symptoms along with significant improvement in the tensile strength of hair, in the mean number of hairs lost after one minute of combing, in the hair follicle count in a selected shaved scalp area. There was also a significant reduction in the number of exclamation point hairs. Furthermore, the sequential scalp biopsies revealed an increase in the number of hair follicles and normal epithelialization. Also, there was a significant improvement in the overall subjective and objective score. Furthermore, there were no clinically significant adverse reactions, with an excellent compliance to the therapy. It may be concluded that “Hair Loss Cream (PCPB Hair Cream)” is effective and safe in the management of telogen effluvium.

ABBREVIATIONS

GCP	:	Good clinical practice
HPE	:	Histopathological examination
HRT	:	Hormone replacement therapy
HS	:	Highly significant
NS	:	Not significant
S	:	Significant
TLC	:	Thin layer chromatography

INTRODUCTION

Hair loss provokes anxiety and distress (more profound than its objective severity would appear to justify), which reflects the symbolic and psychosocial importance of hair.[1] Hair loss is a common disorder that affects men and women of all ages; and about 50% of men and women suffer from hair loss by the age of 40.[2] Androgenetic alopecia and diffuse hair loss (telogen effluvium) are the common causes, while alopecia areata (patchy balding) affects 1.7% of the population.[3]

"Telogen effluvium" develops over a period of several months, is usually, not a permanent form of hair loss, and eventually, the hair follicles can recover. The potential causes of

telogen effluvium include malnutrition and crash dieting, pregnancy and childbirth, UV radiation exposure, drugs, endocrine disorders, extreme physical and emotional stress, and severe systemic illness. Topical application of biological response modifiers, and antiandrogens are currently available therapies for the management of telogen effluvium (in women, HRT can also be used); however, the low success rate and associated adverse effects limit their clinical use.[4]

"Hair Loss Cream (PCPB Hair Cream)" is a polyherbal formulation recommended for the management of telogen effluvium, and contains the extracts of the flowers of *Butea frondosa* and the stem bark of *Butea parviflora*.

Aim of the Study

This study was planned to evaluate the clinical efficacy and safety of "Hair Loss Cream (PCPB Hair Cream)" in the management of telogen effluvium.

Study Design

This study was an open, phase III clinical trial, conducted at the Department of Dermatology of N.H.L. Medical College and V.S. Hospital, Ahmedabad, India from January to August, 2004, as per the ethical guidelines of GCP. The study protocol, case report forms, regulatory documents, product information, and informed consent forms (in Gujrathi and English) were submitted to the "Institutional Ethics Committee", and were approved by the same.

MATERIALS AND METHODS

Inclusion Criteria

A total of 100 patients of both sexes, in the age group of 18-50 years, who were suffering from mild to moderate telogen effluvium, and who were willing to give informed written consent were enrolled in the study.

Exclusion Criteria

Patients on immunosuppressive drugs, patients applying other topical therapy for diffuse hair loss, in the last 2 weeks prior to the initiation of the study, patients with evidence of skin infection and pregnant and lactating women were excluded from the study. Also, those patients who were not willing to give informed written consent were excluded from the study.

Study Procedure

Each patient's demographic medical history (*esp*. local fungal infection, dandruff, pediculosis, trichotillomania, stress, diet, past illness, and drugs), and treatment details were recorded. All the enrolled patients underwent a thorough clinical examination, and scalp skin examination (which included the assessment of number of hairs lost in one-minute combing test, presence of alopecic patch/es, number of exclamation point hairs, hair pull test, epidermal changes and alopecia pattern Viz. "reticular patches" (with extensive hair loss), or "coalescent patches/ophiasis" (with localized hair loss), or "sisaipho" (with hair loss sparing the sides and back of the head). The scalp-specific investigations included microscopic hair examination, Wood's lamp examination, and in a few selected patients, sequential biopsy of the scalp was done for HPE. In all the patients, thorough laboratory investigations were done, which included hematological and biochemical investigations (hemoglobin, total leucocyte count, differential leucocyte count, erythrocyte sedimentation rate, serum creatinine, alkaline phosphate, and transaminase, liver function tests, stool and urine examination, and specific investigations like T3, T4, and thyroid stimulating hormone levels.

All the patients were advised to apply sufficient quantity of "Hair Loss Cream (PCPB Hair Cream)" to the affected area of scalp, daily, at night, for a period of 6 months, with gentle massage, and were advised to leave the "Hair Loss Cream (PCPB Hair Cream)" overnight. Patients were told to restrict themselves to "Hair Loss Cream (PCPB Hair Cream)" as the only treatment for their diffuse hair loss and no other active treatment intervention was allowed.

Follow-up and Monitoring

All the patients were followed up every month for a period of 6 months. At each follow-up visit, evaluation of symptomatic improvement was done, which was followed by scalp examination, hair pull test, and one-minute combing test.

Primary and Secondary Endpoints

The predefined primary efficacy endpoints were improvements in the subjective and objective score. The subjective evaluation was done using global evaluation scores (0=poor, 1=fair, 2=good, and 3=excellent). The objective improvement evaluation included: (1) Mean number of hair lost during one minute combing test (>150 hairs lost=poor, 100-150 hairs lost=fair, 50-100 hairs lost=good and <50 hairs lost= response), (2) Number of hair follicles in a selected shaved one cm^2 of scalp (No increase=poor, 50% increase=fair, 100% increase=good and 200% increase=excellent). Evaluation of overall efficacy was graded as excellent (subjective evaluation score=3 and objective evaluation score=3), good (subjective evaluation score=2 and objective evaluation score=2), fair (subjective evaluation score=1 and objective evaluation score=1), and poor (subjective evaluation score=0 and objective evaluation score=0). The predefined secondary safety endpoints were the incidence of adverse events and overall patient compliance to the therapy.

Adverse Events

All the adverse events were recorded with information about date of onset, severity, duration and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as "*Unrelated*", "*Possible*" and "*Probable*". Patients were allowed to voluntarily withdraw from the study, if they experienced serious discomfort or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance was not regarded as treatment failure and the reasons for non-compliance were noted.

Statistical Analysis

Statistical analysis was done according to intent-to-treat principles. Changes in various parameters from baseline values and values after 1, 2, 3, 4, 5, and 6 months were analyzed by the "*Repeated Measures ANOVA test*", followed by "*Bonferroni's Multiple Comparison Test"*. The minimum level of significance was fixed at 99% confidence limit and a 2-sided *p* value of <0.05 was considered as significant.

RESULTS

A total 100 patients were included in the study, and 3 patients were lost to follow-up. The mean age of patients was 28.07 years, and the mean duration of hair loss was 14.81 months.

There was a significant reduction in the associated symptoms (itching, irritation and dryness of the scalp) within a week, and by the end of fortnight, all these symptoms disappeared. There was a significant improvement in the tensile strength of hair as judged by the pull test,

after one month's period, and the improvement trend continued till the end of the study period.

There was a significant reduction in the mean number of hairs lost after one-minute combing test after each monthly interval from 117.4 to 102.2, 88.89, 80.19, 73.15, 67.22, and 62.96 **(Table 1 and Figure 1)**. Also, there was improvement in the hair follicle count in selected shaved scalp areas from 1.88 after one month to 1.92 after two months, and to 1.96 after three months and a significant improvement to 2.25, 2.55, and 2.85, after subsequent monthly intervals **(Table 2 and Figure 2)**. There was a significant reduction in the number of exclamation point hairs, from the 2nd month onwards, and at the end of study, majority of hair had normal microscopic pattern. In 3 patients, scalp biopsy was done for HPE, which revealed a reduction in the number of hair follicles and damaged epithelium. After two months, a repeat scalp biopsy revealed an increase in the number of hair follicles, alongwith normal epithelialization.

Table 1: Reduction in the mean number of hair lost in one-minute combing test

Parameter	Base-line	1 month	2 months	3 months	4 months	5 months	6 months
Mean	117.4	102.2	88.89	80.19	73.15	67.22	62.96
Std. Deviation	10.23	16.83	24.47	30.43	34.98	39.4	42.68
Std. Error	1.968	3.239	4.709	5.856	6.731	7.583	8.214
Lower 99% CI of mean	111.9	93.22	75.8	63.91	54.44	46.15	40.14
Upper 99% CI of mean	122.9	111.2	102	96.46	91.85	88.3	85.79
Repeated Measures ANOVA Summary	F=48.8, R^2=0.6524, p<0.0001, HS						

Bonferroni's Multiple Comparison Test	**Mean Diff.**	***t***	***p* value**	**Summary**
0 month vs 1 month	15.20	3.81	p<0.01	S
1 month vs 2 months	13.31	3.35	p<0.01	S
2 month vs 3 months	8.70	3.45	p<0.01	S
3 month vs 4 months	7.04	3.75	p<0.01	S
4 month vs 5 months	5.93	3.26	p<0.01	S
5 month vs 6 months	4.26	2.89	p<0.01	S

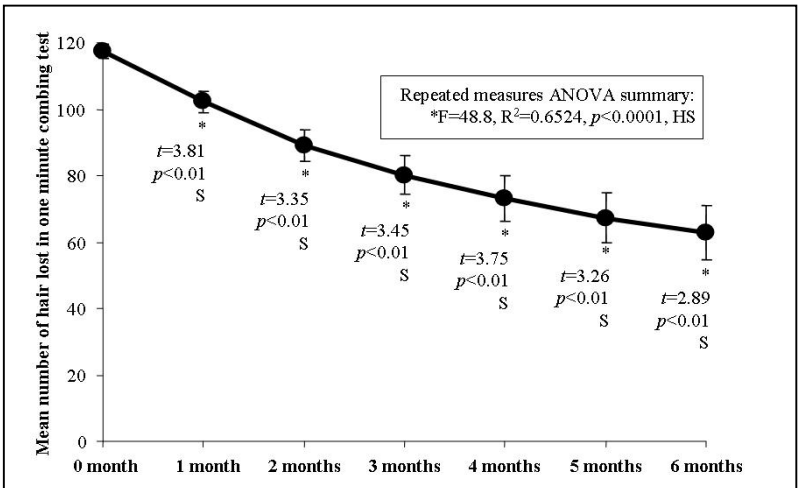

Figure 1: Reduction in the mean number of hair lost in one-minute combing test

There was a significant improvement in the overall subjective and objective evaluation score after each monthly interval from baseline to 1.29, 2.00, 1.96, 2.29, 2.63, and 2.88, **(Table 3 and Figure 3)**. In the overall efficacy evaluation, 84 (86.59%) patients rated the treatment as "excellent" and the rest 13 (13.41%)} patients rated the treatment as "good".

Also, there were no clinically significant adverse reactions, either observed by the investigators or reported by the patients, during the entire study period, and the overall compliance to the therapy was excellent.

Table 2: Improvement in the mean score for hair follicle in a selected shaved one cm^2 patch						
Parameter	**1 month**	**2 months**	**3 months**	**4 months**	**5 months**	**6 months**
Mean	1.88	1.92	1.96	2.25	2.55	2.85
Std. Deviation	0.3203	0.2669	0.44	0.6	0.5064	0.362
Std. Error	0.06163	0.05136	0.08	0.1	0.0975	0.0697
Lower 99% CI of mean	1.718	1.783	1.73	1.9	2.285	2.658
Upper 99% CI of mean	2.06	2.069	2.2	2.6	2.826	3.045
Repeated Measures ANOVA Summary	F=0.5666, R^2=33.99, p<0.0001, HS					

Bonferroni's Multiple Comparison Test	**Mean Difference**	***t***	***p* value**	**Summary**
1 month vs 2 months	0.04	0.3883	p>0.05	NS
2 month vs 3 months	0.04	0.3883	p>0.05	NS
3 month vs 4 months	0.30	3.1070	p<0.05	S
4 month vs 5 months	0.30	3.1070	p<0.05	S
5 month vs 6 months	0.30	3.1070	p<0.05	S

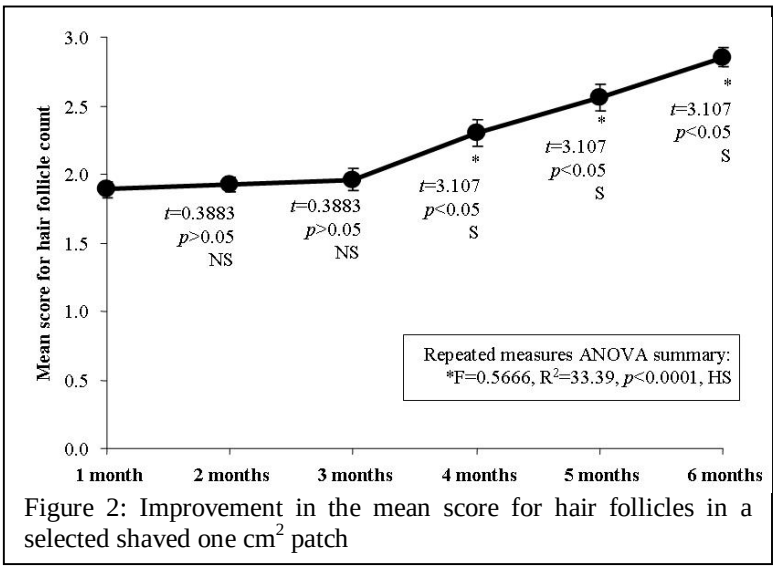

Figure 2: Improvement in the mean score for hair follicles in a selected shaved one cm^2 patch

DISCUSSION

Scalp hairs grow in an asynchronous pattern, with about 80% of hair follicles in growing phase (anagen), while the rest are either in an involuting (catagen) or resting phase (telogen). Hairs in the resting phase fall out after 2 to 3 months, with subsequent growth of new hair. It is normal to shed some hair each day as a part of the hair cycle, and the average daily hair loss is 25 to 100 hair fibers.[5] Alteration of hair growth cycle is clinically manifested as increased shedding of scalp hair, and telogen effluvium is the result of an increased number of resting follicles [6].

Telogen effluvium is a common cause of hair loss, may develop after medication intake, illness, childbirth, and crash dieting.[7] The clinical presentation of telogen effluvium varies from a localized area of thinning to a total body hair loss (alopecia areata universalis), and the incidence of progression to a more widespread loss causing alopecia totalis or alopecia universalis is about 1%.[8]

The diagnosis of hair disorders is complex, and diagnostic techniques include clinical examination (scalp condition, hair loss pattern, length and diameter of hair fibers, hair pulls, one-minute combing test, clipping, plucking, and microscopical examination of hair fibers, scrapings of scalp scales for microbial culture, and a scalp-punch biopsy). Other laboratory

tests, such as a complete blood count (CBC), ferritin measurement (should usually be higher than 40 µg/L to ensure normal hair growth), and thyroid screening are helpful.

Table 3: Subjective and objective evaluation of Hair Loss Cream therapy						
Parameter	**1 month**	**2 months**	**3 months**	**4 months**	**5 months**	**6 months**
Mean	1.29	2.00	1.96	2.29	2.63	2.88
Std. Deviation	0.4653	0.000	0.4369	0.5417	0.4921	0.3203
Std. Error	0.08955	0.000	0.08408	0.1043	0.09471	0.06163
Repeated Measures ANOVA Summary	F=206.5, R^2=0.8881, p<0.0001, HS					
Bonferroni's Multiple Comparison Test	**Mean Difference**		***t***	***p* value**	**Summary**	
1 month vs 2 months	0.7037		7.369	p<0.001	HS	
2 month vs 3 months	0.03704		0.3878	p>0.05	NS	
3 month vs 4 months	0.3333		3.490	p<0.01	S	
4 month vs 5 months	0.3333		3.490	p<0.01	S	
5 month vs 6 months	0.2593		2.715	p<0.05	S	

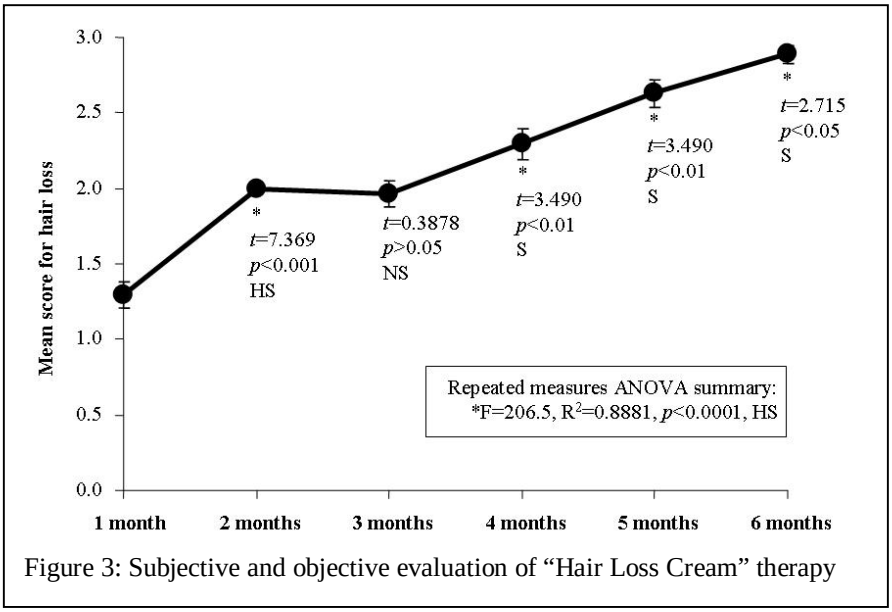

Figure 3: Subjective and objective evaluation of "Hair Loss Cream" therapy

A variety of therapies are available for hair loss, and biological response modifiers (e.g. topical minoxidil), and select antiandrogens are the commonly used treatment options. In women, in addition to antiandrogens, HRT can be used; while the use of systemic corticosteroids is controversial because of their prolonged duration of therapy and potential side effects, which include cataracts, osteopenia, osteoporosis, and growth retardation.[9]

There are numerous limitations for the recommendation of the topical minoxidil therapy. Patients being considered for topical minoxidil therapy require to have a healthy, normal scalp. The common local adverse effects of minoxidil are irritant dermatitis, allergic contact dermatitis, folliculitis, alopecia, hypertrichosis and seborrhea. As enough minoxidil is absorbed systemically from the skin, potential exists for systemic adverse effects (e. g. generalized and local edema, pericardial effusion, pericarditis, tamponade, tachycardia, angina, potentiation of the orthostatic hypotension, etc.). Furthermore, topical minoxidil is absorbed systemically, which is secreted in human milk; hence, nursing women cannot use

topical minoxidil. Also, the safety and effectiveness of topical minoxidil, in patients under than 18 years and over 65 years of age has not been established.

This study observed a significant improvement in the tensile strength of hair, mean number of hairs lost after one-minute combing, hair follicle count in a selected shaved scalp area, with a significant reduction in the number of exclamation point hairs. Furthermore, the sequential scalp biopsies revealed an increase in the number of hair follicles and normal epithelialization. Also, there was a significant improvement in the overall subjective and objective evaluation score, and there were no clinically significant adverse reactions, with an excellent overall compliance to the therapy. These beneficial effects might have been due to the synergistic actions of the ingredients of "Hair Loss Cream (PCPB Hair Cream)".

"Hair Loss Cream (PCPB Hair Cream)" was formulated after extensive bioactive screening.[10] The active ingredients of "Hair Loss Cream (PCPB Hair Cream)" are *Butea frondosa* and *Butea parviflora.* The active ingredients of *Butea frondosa* are flavones and flavonoids (butrine, isobutrine and free amino acids)[11], while the chemical composition of *Butea parviflora* are glycosides and flavonoidses.[11]

In an experimental study, the effect of "Hair Loss Cream (PCPB Hair Cream)" was evaluated in chemotherapy-induced alopecia in cell line model. Synchronized hair cycle were treated with cyclophosphamide, which resulted in complete alopecia followed by hair regrowth (imitating hair follicle response and histopathology seen in human chemotherapy-induced hair loss). The results indicated that "Hair Loss Cream (PCPB Hair Cream)" treatment induced remarkable hair re-growth.[12]

Therefore, it can be postulated that "Hair Loss Cream (PCPB Hair Cream)" induces hair growth in telogen effluvium by acting on dermal papilla and induces hair follicle development from the epidermis, alongwith increase in the size of dermal papilla. It also stimulates the multiplication of hair fibre cells with the stimulation of anagenic phase and reduces catagenic and telogenic phases. Furthermore, Hair Loss Cream (PCPB Hair Cream) improves tensile strength of hair, and improves hair follicular density

CONCLUSION

Hair loss is a common and distressing symptom affecting men and women of all ages. Telogen effluvium is a common cause of hair loss. A variety of therapies are available for the management of telogen effluvium; however, the low success rate and associated adverse effects limit their clinical use. This study was planned to evaluate the efficacy and safety of "Hair Loss Cream (PCPB Hair Cream)" in the management of telogen effluvium.

This study observed a significant reduction in the associated symptoms alongwith a significant improvement in the tensile strength of hair, in the mean number of hairs lost after one-minute combing, in the hair follicle count in a selected shaved scalp area, and also a significant reduction in the number of exclamation point hairs. Furthermore, the sequential scalp biopsies revealed an increase in the number of hair follicles and a normal epithelial pattern. Also, there was a significant improvement in the overall subjective and objective evaluation score and there were no clinically significant adverse reactions, with an excellent overall compliance to the therapy. These beneficial effects might be due to the synergistic effects of the ingredients of the "Hair Loss Cream (PCPB Hair Cream)". Therefore, it may be concluded that "Hair Loss Cream (PCPB Hair Cream)" is effective and safe in the management of telogen effluvium.

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