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Comparative Evaluation of the Efficacy and Tolerability of 4-n-Butylresorcinol Combined with Peptides versus Cysteamine in Patients with Hyperpigmentation: A Prospective Cohort Study

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ABSTRACT

Objective: To compare the efficacy and tolerability of two topical treatment combinations containing 4-n-butylresorcinol, one with peptides and the other with cysteamine, in patients with hyperpigmentation.

Materials and Methods: This hospital-based, single-centre prospective cohort study was conducted in the Dermatology Outpatient Department of Adesh Hospital, Bathinda, Punjab, India. A total of 66 patients aged 18–60 years who had been prescribed either 4-n-butylresorcinol plus peptides or 4-n-butylresorcinol plus cysteamine were included. Treatment outcomes were assessed using patient-reported effectiveness, tolerability, adherence, satisfaction, adverse-effect reporting, and changes in the modified Melasma Area and Severity Index (mMASI) scores. Descriptive statistics were used to summarize patient characteristics and treatment outcomes. The Wilcoxon signed-rank test was reported for pre- and post-treatment mMASI scores, and a chi-square analysis was planned or reported for the association between treatment group and perceived effectiveness.

Results: Of the 66 patients, 42 (63.6%) received 4-n-butylresorcinol plus peptides, while 24 (36.4%) received 4-n-butylresorcinol plus cysteamine. A decrease in mMASI scores was recorded in 61 patients, while five patients had unchanged scores and none had an increase. The proportion of patients with mMASI scores in the 0–2 range increased from 7.6% before treatment to 83.3% after treatment. Overall, 30 patients (45.5%) rated their treatment as effective and 10 (15.2%) as very effective. The proportion rating treatment as effective was 40.5% in the peptide combination group and 54.2% in the cysteamine

combination group. General side effects were reported by nine patients (13.6%), while 64 patients (97.0%) reported that the treatment met their expectations.

Conclusions: Both treatment combinations were associated with improvements in mMASI scores and favourable patient-reported outcomes in this cohort. The proportion of patients reporting an effective response was descriptively higher in the cysteamine combination group. However, the observational design, unequal group sizes, and limitations in statistical reporting prevent a definitive conclusion regarding comparative superiority. Further adequately designed comparative studies are warranted.

Keywords: Hyperpigmentation; melasma; 4-n-butylresorcinol; cysteamine; peptides; mMASI; tolerability; depigmenting therapy.

INTRODUCTION

Hyperpigmentation is characterized by increased or uneven pigmentation of the skin and includes several clinically distinct disorders, among which melasma and post-inflammatory hyperpigmentation (PIH) are particularly relevant in dermatological practice. Melanin has an important photoprotective role, but disturbances in its production or distribution can produce visible pigmentary changes. These disorders are often most apparent on exposed areas of the body and may influence self-confidence and quality of life.

Melasma commonly presents as brown to grey-brown macules or patches on sun-exposed facial areas, particularly the cheeks, forehead, nasal bridge and upper lip. Its pathogenesis is multifactorial and may involve ultraviolet exposure, hormonal influences, genetic predisposition and inflammation. PIH occurs following cutaneous inflammation or injury, including acne, burns and eczema, and may be particularly noticeable in individuals with medium-to-dark skin tones. The chronic nature of these disorders means that sustained treatment and adherence are important components of clinical management.

Hydroquinone has historically been a widely used topical depigmenting agent, but prolonged use and tolerability concerns have stimulated interest in alternative agents and combination regimens. 4-n-butylresorcinol is a resorcinol derivative described in the thesis as an inhibitor of tyrosinase and a promising depigmenting agent. Peptides have been investigated as supportive cosmetic and dermatological ingredients that may influence melanogenesis or melanin transfer while generally being considered suitable for longer-term use. Cysteamine is an endogenous thiol compound that has attracted interest as a depigmenting agent because of its effects on melanogenesis and its potential as an alternative to conventional therapies.

The thesis on which the present manuscript is based evaluated two combination regimens: 4-n-butylresorcinol with peptides and 4-n-butylresorcinol with cysteamine in patients with hyperpigmentation. The study incorporated both an objective pigment measure, the modified Melasma Area and Severity Index (mMASI), and patient-reported measures including perceived effectiveness, tolerability, adherence, manageability and satisfaction. The present article condenses those findings into a journal-style research manuscript.

AIM AND OBJECTIVES

The aim was to compare the efficacy and tolerability of 4-n-butylresorcinol-containing combination therapies using peptides and cysteamine in patients with hyperpigmentation.

- To evaluate the tolerability profile of the depigmenting therapies using patient-reported outcomes and adverse effects.
- To evaluate the efficacy of the depigmenting combinations using treatment response and mMASI scores.
- To compare the observed response between 4-n-butylresorcinol plus peptide and 4-n-butylresorcinol plus cysteamine.

MATERIALS AND METHODS

Study design and setting. This was a hospital-based, single-centre prospective cohort study conducted in the Outpatient Department of Dermatology, Adesh Hospital, Bathinda, following approval from the Scientific Research Committee and the Ethics Committee for Biomedical and Health Research, Adesh University, Bathinda. The thesis describes the study duration as 3 months.

Participants. The final study population comprised 66 patients aged 18–60 years. Eligible patients included those across Fitzpatrick skin types I–VI who had been prescribed 4-n-butylresorcinol-containing therapy with either peptides or cysteamine. Patients with known allergies to the treatment, chronic skin conditions such as psoriasis or eczema, and drug-induced hyperpigmentation associated with agents such as phenytoin or antimalarials were excluded.

Data collection. Written informed consent was obtained before participation. A data collection form, medication-use form and mMASI assessment form were used.

Treatment efficacy was assessed using patient-reported treatment effectiveness, time to notice a change in skin tone and change in mMASI score. Tolerability was evaluated through reported side effects, overall tolerability, treatment manageability, adherence, whether treatment met expectations, satisfaction

and adverse drug reaction (ADR) reporting. The mMASI scoring framework used facial regions with weighted contributions from the forehead, right malar region, left malar region and chin.

Sample size and statistical analysis. The thesis reports the use of Slovin's formula, with a known population of approximately one patient per day, a 5% level of significance and a calculated sample size of 66 patients after accounting for the stated working days.

$n = \frac{N}{1+N(\alpha)^2}$

N = 79

α = 0.05

$n = \frac{79}{1+79(0.0025)}$

n ≈ 66.

Statistical Power Calculation: Post hoc statistical power analysis was conducted using G power for the Wilcoxon signed-rank test. Based on the sample size of 66 patients and an effect size of 0.847, the achieved power was calculated at a 5% level of significance.

Table 1: Calculation of Statistical Power

Test Type	Total sample size	Level of significance	Z-value	Effect size	Statistical power
Wilcoxon signed-rank test	66	5%	6.882	0.847	0.9999997

Data were analysed using Microsoft Excel. Descriptive statistics were expressed as frequencies and percentages. The thesis reports a Wilcoxon signed-rank test for pre- and post-treatment mMASI scores and a chi-square analysis for treatment group versus perceived effectiveness.

Ethical considerations. The study was conducted following institutional research and ethics approval. Participation was voluntary, written informed consent was obtained, data were anonymized and securely stored, and participants were allowed to withdraw without penalty.

RESULTS:

A total of 66 patients were included. The largest age group was 29–39 years (43.9%), followed by 18–28 years (40.9%) and 40–50 years (15.2%). The study population consisted of 52 females (78.8%) and 14 males (21.2%). The recorded Fitzpatrick skin types were type III in 9.1%, type IV in 63.6% and type V in 27.3% of patients.

Table 2. Baseline demographic and treatment characteristics of participants (n = 66)

Variable	Category	n	%
Age	18–28 years	27	40.9
Age	29–39 years	29	43.9
Age	40–50 years	10	15.2
Gender	Male	14	21.2
Gender	Female	52	78.8
Skin type	III	6	9.1
Skin type	IV	42	63.6
Skin type	V	18	27.3
Treatment	4-n-butylresorcinol + peptide	42	63.6
Treatment	4-n-butylresorcinol + cysteamine	24	36.4

Twenty-four patients (36.4%) reported a previous history of skin conditions, whereas 42 (63.6%) did not. Fifteen patients (22.7%) had previously used depigmentation agents. Among those with a previous treatment history, 57 patients overall (86.4%) were recorded in the less-than-one-month category, while 7 (10.6%) had 1–3 months, 1 (1.5%) had 5–6 months, and 1 (1.5%) had more than 6 months.

Table 3. Treatment history and patient-reported response (n = 66)

Outcome	Category	n	%
Previous skin condition	Yes	24	36.4
Previous skin condition	No	42	63.6
Previous depigmentation-agent use	Yes	15	22.7
Previous depigmentation-agent use	No	51	77.3
Previous treatment duration	<1 month	57	86.4

Previous treatment duration	1–3 months	7	10.6
Previous treatment duration	5–6 months	1	1.5
Previous treatment duration	>6 months	1	1.5
Perceived effectiveness	Slightly effective	2	3.0
Perceived effectiveness	Moderately effective	24	36.4
Perceived effectiveness	Effective	30	45.5
Perceived effectiveness	Very effective	10	15.2

A change in skin tone was noticed within 2 weeks by 21 patients (31.8%), within 2–4 weeks by 25 (37.9%) and within 1–3 months by 20 (30.3%). Nine patients (13.6%) reported side effects in the general side-effect assessment. Overall tolerability was rated as fair by 6.1%, good by 30.3%, very good by 53.0% and excellent by 10.6%.

Table 4. Tolerability and patient-reported treatment experience

Outcome	Category	n	%
Change in skin tone	Within 2 weeks	21	31.8
Change in skin tone	2–4 weeks	25	37.9
Change in skin tone	1–3 months	20	30.3
Side effects	Yes	9	13.6
Side effects	No	57	86.4
Overall tolerability	Fair	4	6.1
Overall tolerability	Good	20	30.3
Overall tolerability	Very good	35	53.0
Overall tolerability	Excellent	7	10.6
Manageable in daily life	Yes	59	89.4
Manageable in daily life	No	7	10.6
Recommended to others	Yes	61	92.4

Recommended to others	No	5	7.6

Adherence was reported as always in 47 patients (71.2%), often in 17 (25.8%) and sometimes in 2 (3.0%). Only 5 patients (7.6%) reported difficulty with adherence. Expectations were recorded as complete reduction for 57 patients (86.4%), moderate reduction for 7 (10.6%) and mild reduction for 2 (3.0%). Sixty-four patients (97.0%) reported that treatment met their expectations and were satisfied with the result.

In the ADR assessment, 10 patients (15.2%) were recorded as reporting an ADR and 56 (84.8%) did not report an ADR. The thesis therefore contains two related but different tolerability percentages—13.6% for the general side-effect item and 15.2% for the ADR item—and these are retained separately in this manuscript rather than being combined.

Table 5. Distribution of mMASI scores before and after treatment

mMASI range	Before n (%)	After n (%)
0–2	5 (7.6)	55 (83.3)
2–4	7 (10.6)	8 (12.1)
4–6	17 (25.8)	3 (4.5)
6–8	30 (45.5)	0 (0.0)
8–10	7 (10.6)	0 (0.0)
Total	66 (100.0)	66 (100.0)

The Wilcoxon signed-rank analysis showed that 61 patients had a decrease in mMASI score after treatment, no patient had an increase, and 5 patients had unchanged scores. The reported test statistic was $Z = -6.882$. The thesis reports $p = 0.05$ in its interpretation; this manuscript retains the thesis-reported value of $p = 0.05$ for consistency with the submitted study report.

When effectiveness was examined by treatment group, 18 of 42 patients (42.9%) receiving 4-n-butylresorcinol plus peptide were classified as moderately effective, 17 (40.5%) as effective and 7 (16.7%) as very effective. In the 4-n-butylresorcinol plus cysteamine group, 2 of 24 patients (8.3%) were classified as slightly effective, 6 (25.0%) as moderately effective, 13 (54.2%) as effective and 3 (12.5%) as very effective. The thesis describes the chi-square analysis as indicating a higher proportion of

effective responses in the cysteamine group; because the available thesis text does not report the chi-square statistic or p-value, no inferential significance claim is made here.

Table 6. Patient-reported effectiveness by treatment combination

Treatment combination	Slightly effective n (%)	Moderately effective n (%)	Effective n (%)	Very effective n (%)	Total
4-n-butylresorcinol + peptide	0 (0.0)	18 (42.9)	17 (40.5)	7 (16.7)	42
4-n-butylresorcinol + cysteamine	2 (8.3)	6 (25.0)	13 (54.2)	3 (12.5)	24
Total	2 (3.0)	24 (36.4)	30 (45.5)	10 (15.2)	66

DISCUSSION

The present prospective cohort study evaluated two 4-n-butylresorcinol-containing combination therapies in 66 patients with hyperpigmentation. The study population was predominantly female and was largely composed of patients with Fitzpatrick skin types IV and V. This distribution is consistent with the clinical relevance of hyperpigmentation in darker skin types, where pigmentary disorders such as melasma and PIH may be particularly visible.

The treatment combinations were not equally represented: 42 patients received 4-n-butylresorcinol plus peptide and 24 received 4-n-butylresorcinol plus cysteamine. Overall patient-reported effectiveness was favourable, with 45.5% describing treatment as effective and a further 15.2% describing it as very effective. Changes in skin tone were noticed by most participants within the first 1–3 months, with 69.7% reporting a visible change within the first 4 weeks.

The objective mMASI findings support the patient-reported improvement. Sixty-one of 66 patients demonstrated a reduction in mMASI score, whereas none showed an increase and five remained unchanged. The proportion of patients with an mMASI score of 0–2 increased from 7.6% before treatment to 83.3% after treatment. The thesis reports a Wilcoxon signed-rank Z value of −6.882 with $p = 0.05$, indicating a statistically significant pre- to post-treatment difference according to the study's reported analysis.

The treatment-group distribution showed a higher proportion of patients classified as 'effective' in the 4-n-butylresorcinol plus cysteamine group (54.2%) than in the peptide group (40.5%). However, this finding should be interpreted cautiously because the groups were unequal in size, the study was observational rather than randomized, and the available thesis does not report the chi-square p-value. The observed difference therefore represents a descriptive group comparison rather than definitive evidence that one regimen is superior.

Tolerability findings were favourable. General side effects were reported by 13.6% of patients, while 15.2% were recorded as having an ADR in the separate ADR assessment. Most patients rated tolerability as very good or excellent, and 89.4% considered the treatment manageable in daily life. Adherence was also high, with 71.2% reporting always adhering to treatment and only 7.6% reporting difficulty with adherence. Patient satisfaction was 97.0%, and 92.4% stated that they would recommend the treatment to others.

These findings are broadly aligned with the rationale described in the thesis literature review. Earlier literature cited in the thesis discusses the established role of hydroquinone, the importance of combination therapy, the use of 4-n-butylresorcinol in melasma, and the potential of peptides and cysteamine as alternative or supportive depigmenting approaches. A randomized double-blind study cited in the thesis specifically evaluated 4-n-butylresorcinol 0.3% cream for melasma, while reviews have considered the efficacy and tolerability of non-hydroquinone therapies.

The study has several limitations. It was single-centre and observational, with a relatively small sample size and unequal treatment-group allocation. The thesis also reports a 6-month overall duration but a 3-month sample-size/data-collection period, which should be clarified in the final journal submission. In addition, microbiological or instrumental pigment measurements beyond mMASI were not described, and the ADR assessment did not provide a detailed breakdown of individual reactions in the results section. Larger, adequately powered comparative studies with standardized treatment duration, detailed adverse-event characterization and longer follow-up are needed.

CONCLUSION

In this hospital-based prospective cohort of 66 patients with hyperpigmentation, both 4-n-butylresorcinol plus peptide and 4-n-butylresorcinol plus cysteamine combinations were associated with favourable clinical and patient-reported outcomes. A substantial reduction in mMASI scores was observed after treatment, with 61 patients showing improvement and no patient showing an increase in score. Treatment was generally well tolerated, adherence was high and patient satisfaction was substantial. The

cysteamine-containing combination showed a higher proportion of patients classified as 'effective' in the descriptive group comparison; however, this observation should not be interpreted as definitive comparative superiority because of the study's observational design, unequal group sizes and incomplete reporting of inferential statistics. Further controlled studies with larger samples and standardized follow-up are warranted.

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FUNDING

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ETHICS STATEMENT

The thesis states that the study received approval from the Scientific Research Committee and the Ethics Committee for Biomedical and Health Research, Adesh University, Bathinda, and that written informed consent was obtained from all participants. The specific approval number was not provided in the thesis text available for manuscript preparation.

CONFLICT OF INTEREST

The thesis does not report any conflict of interest.

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