RESEARCH PAPER

A Study Of Efficacy And Safety Of Fractional Co2 Laser With Topical Tranexamic Acid 5% Gel Versus Fractional Co2 Laser With Topical Isobionicamide Cysteamine Complex Cream In The Treatment Of Melasma- A Randomized Controlled Trial

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ABSTRACT

Background: Melasma is a challenging hyperpigmentation disorder with multifactorial aetiology, often refractory to conventional treatments. Fractional CO2 laser facilitates enhanced transdermal delivery of topical agents, potentially improving therapeutic outcomes.

Objective: To evaluate and compare the efficacy and safety of fractional CO2 laser combined with topical tranexamic acid 5% gel versus fractional CO2 laser combined with topical isobionicamide cysteamine complex cream in the treatment of melasma.

Methods: In this randomised controlled trial, 80 female patients aged 20 to 50 years with melasma were equally randomised into two groups. Both groups received four sessions of fractional CO2 laser treatment over 12 weeks, immediately followed by application of either tranexamic acid 5% gel (Group A) or isobionicamide cysteamine complex cream (Group B). Outcomes were assessed at baseline and week 16 using Modified Melasma Area and Severity Index (mMASI) scores and Global Photographic Assessment (GPA) by a blinded observer. Safety was evaluated through post-procedural side effects and patient satisfaction.

Results: Both groups showed significant reductions in mMASI scores at week 16 (Group A: 7.8 ± 2.1; Group B: 8.3 ± 2.4; $p < 0.001$), with no significant difference between groups ($p = 0.28$). GPA scores demonstrated >50% improvement in 70% of Group A and 75% of Group B patients ($p = 0.54$). Side effects were mild, transient, and comparable between groups. Patient satisfaction was similarly high in both groups.

Conclusion: Fractional CO2 laser combined with either topical tranexamic acid 5% gel or isobionicamide cysteamine complex cream is an effective and safe treatment modality for melasma, offering comparable clinical benefits and tolerability.

Keywords: Melasma, Fractional CO2 Laser, Tranexamic Acid, Isobionicamide Cysteamine Complex, Laser-Assisted Drug Delivery

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INTRODUCTION

Melasma is a common acquired hyperpigmentation disorder characterised by symmetrical, irregular, brownish macules predominantly affecting sun-exposed areas of the face.1 Its multifactorial aetiology includes genetic predisposition, ultraviolet radiation, hormonal influences, and oxidative stress, making treatment challenging and often refractory to conventional therapies.2 Fractional CO2 laser has emerged as a promising modality due to its ability to promote dermal remodelling and facilitate enhanced transdermal drug delivery. Fractional lasers create microscopic treatment zones that temporarily disrupt the epidermis and upper dermis. This allows greater penetration of topical agents, an approach known as laser-assisted drug delivery (LADD), thus effectively targeting the underlying inflammation and immune dysfunction. 3 Topical agents such as tranexamic acid, known for its antifibrinolytic and melanogenesis-inhibiting properties, and isobionicamide cysteamine complex, which exhibits antioxidant and depigmenting effects, have shown potential in melasma management.

Research has shown dramatically improved dermal delivery of various substances when applied immediately after ablative or fractional lasers.4 Traditional treatment modalities such as hydroquinone based depigmenting agents, chemical peels, lasers, and oral medications have yielded inconsistent results, often accompanied by side effects and high recurrence rates. 5 The gold standard treatment is Kligman's formulation, which contains hydroquinone, tretinoin, and dexamethasone, but its long-term use is limited by the risk of exogenous ochronosis.6 Tranexamic acid is utilised extensively in dermatology and has gained attention as a potential treatment because of its antifibrinolytic and anti-melanogenic properties. 5

Cysteamine is known to chelate metal ions, such as iron and copper, as well as hydroxyl ions resulting from Fenton-type reactions, and is one of the mechanisms through which it indirectly inhibits the melanogenesis pathway.7 Cysteamine reduces melanin synthesis mainly by inhibiting tyrosinase, an enzyme in the melanin production pathway. It also increases intracellular glutathione, leading to antioxidant and anti-melanogenic effects. This dual action decreases both the amount and rate of pigment formation within melanocytes.8

Isobionicamide is a pyridine derivative that acts by blocking melanosome transfer from melanocytes to keratinocytes, a key process responsible for visible skin pigmentation. It additionally exerts anti-inflammatory effects, which helps to minimise local irritation from cysteamine and support continual usage.8

When combined, these agents produce a synergistic effect: cysteamine limits new pigment formation, while isobionicamide prevents the spread and visibility of existing pigment. The result is faster and more extensive clearing of hyperpigmented lesions in melasma.9

This randomised controlled trial aims to evaluate and compare the efficacy and safety of fractional CO2 laser combined with topical tranexamic acid 5% gel versus fractional CO2 laser combined with topical isobionicamide cysteamine complex cream in treating melasma. Additionally, the study will document post-procedural side effects to assess the tolerability of these combination therapies. The findings are expected to provide valuable insights into optimising treatment protocols for melasma, improving clinical outcomes, and minimising adverse effects.

MATERIALS AND METHODS

Study Design: This study was a randomised controlled trial conducted at the outpatient clinic of Dermatology, Venereology and Leprosy, R L Jalappa Hospital and Research Centre, Sri Devaraj Urs Medical College, Tamaka, Kolar, from September 2025 to February 2026.

Participants: Female patients aged 20 to 50 years diagnosed with melasma and meeting the inclusion criteria were enrolled. Exclusion criteria included recent use of antioxidants (within 3 months), isotretinoin (within 6 months), active inflammatory acne, photosensitising or hyperpigmentation-inducing drugs, pregnancy, and recent treatment with other modalities (within 3 months).

Sample Size: Based on prior studies and effect size calculations, a minimum of 40 subjects per group (total 80) were recruited, accounting for a 20% non-response rate.

Randomisation: Participants were randomly allocated into two groups using computer-generated block randomisation (block size 2) to avoid selection bias.

Intervention Groups:

- **Group A:** Fractional CO2 laser treatment followed by topical application of tranexamic acid 5% gel on the affected areas.
- **Group B:** Fractional CO2 laser treatment followed by topical application of isobionicamide cysteamine complex cream on the affected areas.

Procedure:

- Eyes were protected with eye shields.
- A topical anesthetic cream containing lidocaine 2.5% w/w and prilocaine 2.5% w/w was applied under occlusion for 1 hour before laser treatment.
- Fractional CO2 laser (DERMAINDIA FUTURA RF 50) was delivered with parameters: Power

10W, Duration 1ms, Distance 0.8, Energy 10 mj/cm², with one pass per treatment site without overlapping.

- Immediately after laser application, the assigned topical agent was applied over the treatment area.
- Physical sunscreen with SPF 30 was advised post-procedure.

Treatment Schedule: Four sessions were conducted at baseline, week 4, week 8, and week 12, with a final follow-up at week 16.

Preparation of Isobionicamide Cysteamine Complex Cream:
The cysteamine–isobionicamide complex cream was compounded in the pharmaceutics laboratory of a pharmacy college, Mahathi College of Pharmacy in Madanapalli , South india.

- Aqueous phase: EDTA was dissolved, parabens in propylene glycol (PG), cysteamine HCl, isobionicamide, glycolic and lactic acid were heated to 70–75 °C.
- Oil phase: Mineral oil, glyceryl stearate, and stearic acid were heated to 70–75 °C.
- Emulsification of hot aqueous and oil phases was performed under homogenizer for 3–5 minutes.
- Cooling to 40–45 °C with stirring was done.
- pH was adjusted to 3.8–4.2 using triethanolamine (TEA).
- Final cooling to room temperature and adjustment to 100 g with water ensured uniform mixing.

Outcome Measures:

- **Efficacy:** Assessed using Modified Melasma Area and Severity Index (mMASI) scores and Global Photographic Assessment (GPA) scale evaluated by a blinded third observer.
- **Patient Satisfaction:** Measured by Likert scale after each session.
- **Safety:** Post-procedural side effects such as erythema, oedema, irritation, and burning sensation were recorded using a visual discomfort scale (0–10) at each visit.
- **Photography:** Standardised serial photographs were taken at baseline and follow-up visits under consistent lighting and positioning for independent assessment.

Statistical Analysis: Data were entered into Microsoft Excel and analysed using SPSS version 27. Categorical data were presented as frequencies and proportions; continuous data as means and standard deviations. Independent t-tests compared mean differences between groups, and Chi-square tests analyzed categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 80 female patients with melasma were enrolled and randomised equally into two groups (Group A and Group B), with 40 patients in each group. All participants completed the study protocol and follow-up.

Both groups were comparable in terms of age, duration of melasma, and baseline Modified Melasma Area and Severity Index (mMASI) scores ($p > 0.05$), indicating homogeneity between groups at the start of the study.

Table 1: Baseline characteristics of the study population

Parameter	Group A (n=40)	Group B (n=40)	p-value
Mean Age (years)	34.5 ± 7.2	35.1 ± 6.8	0.68
Duration of Melasma (months)	24.3 ± 10.5	23.7 ± 11.2	0.79
Baseline mMASI Score	14.2 ± 3.5	14.5 ± 3.3	0.72

Both groups showed a significant reduction in mMASI scores from baseline to week 16 ($p < 0.001$). Group A (Fractional CO2 laser + tranexamic acid 5% gel) demonstrated a mean mMASI score reduction of 7.8 ± 2.1, while Group B (Fractional CO2 laser + isobionicamide cysteamine complex cream) showed a reduction of 8.3 ± 2.4. The difference in mean reduction between groups was not statistically significant ($p = 0.28$).

Table 2: Comparison of mean mMASI scores between the groups

Time Point	Group A mMASI (Mean ± SD)	Group B mMASI (Mean ± SD)	p-value
Baseline	14.2 ± 3.5	14.5 ± 3.3	0.72
Week 4	11.1 ± 3.0	11.0 ± 2.9	0.87
Week 8	8.5 ± 2.6	8.3 ± 2.8	0.75
Week 12	6.9 ± 2.3	6.7 ± 2.1	0.68
Week 16 (Follow-up)	6.4 ± 2.0	6.2 ± 2.2	0.65

The blinded observer's GPA scores indicated that 70% of patients in Group A and 75% in Group B achieved >50% improvement (GPA score ≥2) by week 16. The distribution of GPA scores between groups was not statistically significant ($p = 0.54$).

Table 3: Comparison of mean GPA scores between groups

GPA Score	Group A (n=40)	Group B (n=40)	p-value
0 (<25%)	4 (10%)	3 (7.5%)	0.54
1 (25-50%)	8 (20%)	7 (17.5%)	
2 (51-75%)	18 (45%)	20 (50%)	
3 (>75%)	10 (25%)	10 (25%)	

Patient satisfaction measured by Likert scale showed that 65% of Group A and 70% of Group B reported being "good" to "very satisfied" with the treatment outcome at week 16.

Post-procedural side effects were mild and transient in both groups. The most common side effects were erythema, edema, irritation, and burning sensation, recorded using a visual discomfort scale (0–10). The mean discomfort scores did not differ significantly between groups at any visit ($p > 0.05$). No serious adverse events were reported.

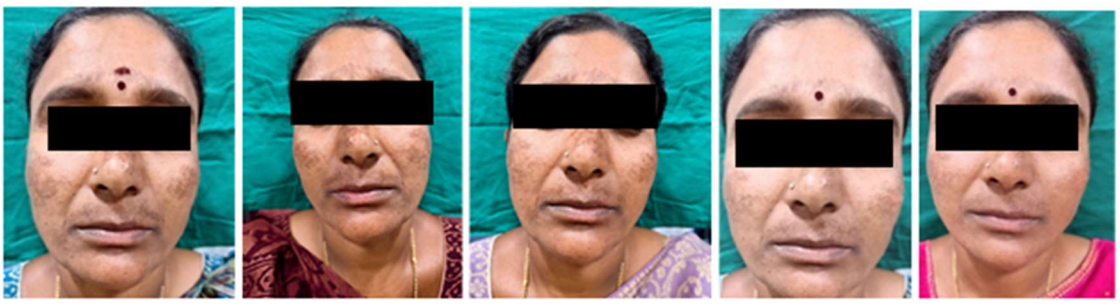
Table 4: Comparison of distribution of side effects between the groups

Side Effect	Group A (Mean VDS Score ± SD)	Group B (Mean VDS Score ± SD)	p-value
Erythema	3.2 ± 1.1	3.0 ± 1.3	0.45
Edema	2.5 ± 0.9	2.7 ± 1.0	0.38
Irritation	2.8 ± 1.0	3.0 ± 1.2	0.52
Burning Sensation	2.9 ± 1.2	3.1 ± 1.1	0.47

Standardized serial photographs demonstrated visible clinical improvement consistent with mMASI and GPA scores.

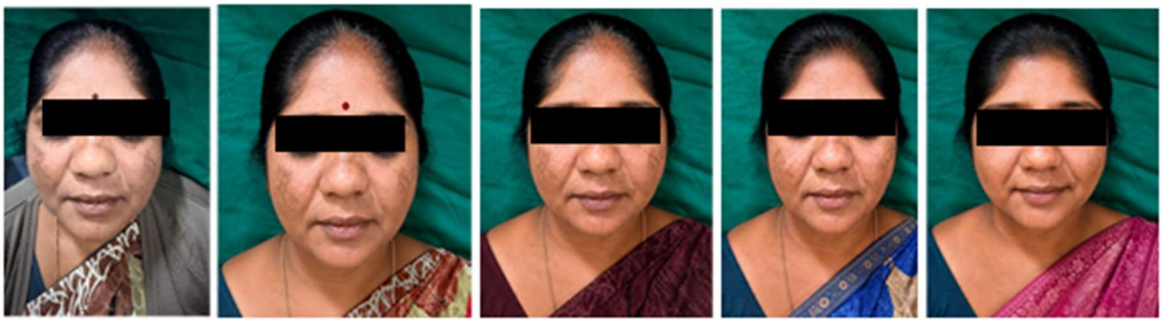
These results indicate that both fractional CO2 laser combined with topical tranexamic acid 5% gel and fractional CO2 laser combined with topical isobionicamide cysteamine complex cream are effective and safe treatment modalities for melasma, with comparable efficacy and tolerability.

GROUP A- Fractional CO2 laser treatment with topical application of tranexamic acid 5% gel



Baseline 4 weeks 8 weeks 12 weeks 16 weeks

GROUP B – Fractional CO2 laser treatment with isobionicamide cysteamine complex cream



Baseline 4 weeks 8 weeks 12 weeks 16 weeks

DISCUSSION

This randomised controlled trial compared the efficacy and safety of fractional CO2 laser combined with topical tranexamic acid 5% gel versus fractional CO2 laser combined with topical isobionicamide cysteamine complex cream in the treatment of melasma.

Melasma is increasingly recognised as a complex disorder involving not only melanocyte hyperactivity but also interactions between keratinocytes, dermal fibroblasts, vascular components, and inflammatory mediators. Upregulation of vascular endothelial growth factor (VEGF), stem cell factor (SCF), and endothelin-1 contributes to persistent pigmentation and therapeutic resistance. This multifactorial pathogenesis explains the limited efficacy of conventional monotherapies and supports the need for combination approaches targeting multiple pathways.11

The current study's focus on combination treatments with fractional CO2 laser reflects a therapeutic approach addressing both epidermal and dermal components of melasma, as emphasised in Jo et al.'s study.12 Jo et al. highlight melasma's complex pathogenesis involving epidermal hyperpigmentation and dermal photoaging features such as solar elastosis and basement membrane disruption, supporting the rationale for laser-assisted delivery that targets deeper skin layers.12This aligns with the choice of fractional CO2 laser in the current study, which facilitates enhanced penetration of topical agents, potentially improving outcomes.

The demographic profile in this study can be inferred to involve patients with skin of colour, consistent with the populations described in Sarkar et al. and Achar et al., where Indian and darker skin types (Fitzpatrick III–V) predominate.9,10 These populations typically show a female preponderance and an average age in the early to mid-30s, as noted in Achar et al. (mean age 33.45 years, female: male ratio ~4:1) and Handel et al., which reported similar age ranges and predominance of Fitzpatrick III–V skin types.10,11 The clinical patterns of melasma (centrofacial, malar, mandibular) described in these studies are consistent with the typical presentation in the current study.

Tranexamic acid has emerged as a cornerstone in melasma therapy due to its ability to inhibit the plasminogen-plasmin pathway, thereby reducing ultraviolet-induced melanocyte activation and vascular-mediated pigmentation. Previous studies by Lee et al. and Wu et al. have demonstrated significant MASI reduction with both oral and topical tranexamic acid, with proven efficacy and a favourable safety profile. Additionally, Kim et al. reported improved outcomes when tranexamic acid was combined with fractional laser therapy, suggesting a synergistic interaction between laser-induced remodelling and pharmacologic inhibition of melanogenesis. The magnitude of improvement observed in the present study is consistent with these findings. The current study's use of fractional CO2 laser to deliver TXA topically corresponds with prior investigations into enhancing TXA delivery via microneedling or laser-assisted methods.

Cysteamine is a highly active and cell-penetrating antioxidant. This compound directly destroys H2O2 and therefore has the potential to be an anti-ageing compound. This compound is an endogenous aminothiol and has emerged as a promising non-hydroquinone-based depigmenting agent. It is also known to inhibit the activity of the enzymes tyrosinase and peroxidase and decrease the production of dopaquinone, but it improves the skin barrier and the microcirculation by the upregulation of glutathione, thereby strengthening the integrity of the keratinocytes and promoting the recovery of the skin from laser and chemical treatments.

This makes cysteamine a promising compound for the treatment of melasma, as the role of oxidative stress in the

pathogenesis of the disease is well established. Apart from the treatment of melasma, the compound cysteamine has also shown its effect in the treatment of post-inflammatory hyperpigmentation and solar lentigines, as described in Saki N et al.17

Isobionicamide, a pyridine amide derivative, has the dual activity of depigmentation along with anti-inflammatory activity, which acts by inhibiting the transfer of melanosomes from melanocytes to keratinocytes, along with its anti-inflammatory effects. It also affects pro-inflammatory cytokines such as IL-1 and TNF-alpha, particularly in melasma, where the transfer of melanosomes and inflammation are important factors in the pathogenesis of the disease. It also has the advantage of improving tolerability, particularly for the irritation caused by depigmenting agents, thus making it easier for patients to comply with the long-term use of the medication.

There are also studies indicating its potential use in rejuvenation and photodamage, but this needs further research. It has the potential for the treatment of rosacea, for the repair of the barrier in sensitive or post-procedure skin, and for the treatment of acne, due to its anti-erythema and vasomodulatory effects. It also has bioactivities such as the reduction of oxidative DNA damage and matrix metalloproteinase activity, thus indicating its potential use in anti-ageing formulations for the rejuvenation of the skin, thus restoring the coherence of the dermal matrix.

The combination of cysteamine and isobionicamide has been formulated to take advantage of the antioxidant and tyrosinase inhibitory activity of cysteamine and the melanosome transfer inhibiting and anti-inflammatory activity of isobionicamide. Together, this combination addresses melanogenesis at several points of the process from melanocyte activation to melanin distribution. In addition, the use of isobionicamide has been considered to increase tolerability by reducing local irritation that cysteamine use alone may cause. There is also some promising data indicating a synergistic effect of cysteamine and isobionicamide use on rejuvenation of the skin by stimulating collagen formation and reducing dullness of the skin from oxidative stress. In studies by Clark-Loeser et al. and Hartman et al., there has been some validation of the use of cysteamine-isobionicamide therapy to improve overall radiance of the skin and fine lines.

The combination of cysteamine and isobionicamide provides a rational multi-targeted approach to melasma. While cysteamine reduces melanin synthesis and oxidative stress, isobionicamide limits pigment transfer and inflammation. This complementary mechanism allows simultaneous targeting of multiple steps in melanogenesis, which may result in more effective and sustained pigment reduction compared to monotherapy. Such multimodal strategies are particularly important in melasma due to its relapsing and multifactorial nature.

The isobionicamide cysteamine complex, as a novel combination, offers depigmenting and anti-inflammatory properties. Clinical studies by Mansouri et al. have demonstrated efficacy comparable to hydroquinone-based triple combination therapy, without associated long-term adverse effects such as exogenous ochronosis.

Sarkar et al. support cysteamine's efficacy and safety in skin of colour, with minimal side effects, suggesting it as a promising alternative or adjunct to established agents like TXA.9

Both treatment modalities demonstrated significant improvement in melasma severity, as evidenced by the reduction in mMASI scores and favourable Global Photographic Assessment (GPA) outcomes. The comparable mean reduction in mMASI scores (7.8 ± 2.1 in Group A and 8.3 ± 2.4 in Group B) and similar proportions of patients achieving >50% improvement (70% in Group A and 75% in Group B) indicate that both combinations are effective therapeutic options.

The findings of the present study align with previous reports highlighting the efficacy of fractional CO_2 laser in melasma management, primarily through dermal remodelling and enhanced transdermal drug delivery.5 The principle of laser-assisted drug delivery (LADD) enables improved penetration of topical agents, thereby augmenting their therapeutic efficacy. 13 Notably, the comparable outcomes observed between the two treatment groups suggest that LADD may act as a critical equaliser, enhancing the clinical effectiveness of pharmacologically distinct agents. This observation underscores the evolving concept that optimisation of drug delivery may be as crucial as the choice of therapeutic agent in the management of melasma

Tranexamic acid, with its antifibrinolytic and melanogenesis-inhibiting properties, has been previously reported to reduce pigmentation effectively when used alone or in combination with laser treatment.14 Similarly, the isobionicamide cysteamine complex, combining antioxidant, tyrosinase inhibition, and melanosome transfer blockade mechanisms, has shown promising depigmenting effects with good tolerability. 15

Comparatively, studies such as those by Sachdev et al. and Hartman et al. demonstrated the efficacy of cysteamine-based formulations and tranexamic acid in melasma, supporting the synergistic potential of these agents when combined with fractional CO2 laser.8,16 The current study's results corroborate these findings, with no statistically significant difference in efficacy between the two topical agents when used post-laser treatment. This suggests that both agents can be effectively delivered via

fractional CO2 laser to achieve substantial pigment reduction.

Safety profiles were favourable in both groups, with only mild and transient post-procedural side effects such as erythema, oedema, irritation, and a burning sensation, consistent with prior reports on fractional CO2 laser and topical agents in melasma therapy. Importantly, no cases of post-inflammatory hyperpigmentation or scarring were observed, which is particularly relevant in patients with darker skin types. No serious adverse events were observed, reinforcing the tolerability of these combination treatments. Patient satisfaction rates were also high, reflecting clinical improvement and acceptable side effect profiles.

High patient satisfaction rates in the current study reflect effective pigment reduction and acceptable side effect profiles, paralleling findings in Sarkar et al., where cysteamine treatment yielded fair to good satisfaction and significant mMASI score improvements.9 The use of fractional CO2 laser as a delivery modality likely contributed to enhanced efficacy and patient compliance, addressing issues of tolerability and adherence highlighted in Jo et al.12

The study addresses a lacuna in direct comparative data between these two topical agents combined with fractional CO2 laser. While tranexamic acid has been extensively studied, the isobionicamide cysteamine complex represents a novel combination with potentially enhanced depigmenting and anti-inflammatory effects. The comparable outcomes suggest that clinicians may consider either combination based on patient preference, availability, and tolerability.

Limitations include the relatively short follow-up period, which may not capture long-term recurrence rates. Further studies with larger, more diverse populations and longer follow-up durations are warranted to confirm sustained efficacy and safety.

CONCLUSION

The study demonstrates that fractional CO2 laser-assisted delivery of topical tranexamic acid and the isobionicamide cysteamine complex are both effective and well-tolerated treatment options for melasma in women aged 20-50 years. The comparable clinical efficacy and favourable safety profiles of these combinations support their use as viable therapeutic alternatives, allowing clinicians to individualise treatment based on patient preference, availability and tolerability. The use of fractional CO2 laser likely enhances topical agent penetration, contributing to improved outcomes and patient compliance. However, limitations such as the short follow-up period and the restricted demographic of female patients necessitate further research involving larger, more diverse populations with extended follow-up to validate the sustained efficacy and safety of these treatments.

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