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**ORIGINAL RESEARCH**

# Split-Face Randomized Study: Low-Fluence QS-Nd:YAG Laser Plus Hydroquinone Cream vs. Hydroquinone Alone for Melasma

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## ABSTRACT

**Background:** Melasma is a common pigmentary disorder predominantly affecting individuals with darker skin types. Although hydroquinone remains the gold standard treatment, its limitations, including slow onset, recurrence, and adverse effects, have prompted the exploration of adjunctive therapies such as low-fluence QS-Nd:YAG lasers. **Methods:** This prospective, split-face randomized controlled trial was conducted on 30 patients with dermal or mixed-type melasma. One side of the face received combination therapy with low-fluence QS-Nd:YAG laser (1064 nm) and 2% hydroquinone cream, while the other side was treated with 2% hydroquinone cream alone. Modified Melasma Area Severity Index (mMASI) scores, clinical photographs, and patient satisfaction were assessed at baseline, 6 weeks, and 10 weeks. Adverse effects were also recorded. **Results:** Combination therapy demonstrated greater short-term efficacy, with 63.6% of patients showing improvement compared to 31.8% on the hydroquinone-only side ($p = 0.034$). The mean mMASI score on the combination-treated side decreased significantly at 6 weeks ($1.36 \pm 0.51$ to $0.95 \pm 0.45$, $p = 0.001$). However, rebound hyperpigmentation occurred in 36.4% of patients on the combination-treated side, and transient erythema was noted in all laser-treated patients. Patient satisfaction was low, with only 31.8% satisfied with laser treatment. **Conclusion:** While the combination of low-fluence QS-Nd:YAG laser and 2% hydroquinone cream showed superior short-term efficacy compared to hydroquinone monotherapy, the benefits were not sustained, and adverse effects were more frequent. Caution is advised when using this combination therapy, with a focus on maintenance strategies and patient counselling to mitigate risks.

**Keywords:** Melasma, QS-Nd:YAG laser, Hydroquinone cream, Low-fluence laser, Hyperpigmentation, Combination therapy, mMASI.



## INTRODUCTION

Melasma, a common acquired hyperpigmentary disorder, significantly impacts individuals' quality of life due to its persistent and often refractory nature. It is particularly prevalent among those with darker skin tones (Fitzpatrick types IV–VI) and typically affects sun-exposed areas such as the cheeks, forehead, and upper lip. The condition disproportionately affects women and is linked to hormonal fluctuations, UV exposure, and genetic predispositions.[1]

Hydroquinone remains the gold standard for treating melasma due to its effectiveness in inhibiting melanogenesis.[1] However, long-term use is associated with challenges such as irritation, ochronosis, and limited efficacy in dermal and mixed melasma. Consequently, adjunctive treatments like laser therapies have gained traction. Among these, the Q-switched Nd:YAG (QS-Nd:YAG) laser has emerged as a promising modality for its ability to target dermal and epidermal melanin with minimal damage to surrounding tissue.[2]

Low-fluence QS-Nd:YAG laser, particularly at 1064 nm, has demonstrated efficacy in reducing melasma severity when used in combination with topical agents. Studies indicate that combination therapies outperform monotherapy, as lasers provide deeper

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melanin clearance while topicals prevent repigmentation.[3] However, treatment with lasers is not without risks, including rebound hyperpigmentation and erythema, necessitating careful evaluation.[4]

The current study aims to compare the efficacy and safety of low-fluence 1064 nm QS-Nd:YAG laser combined with 2% hydroquinone cream versus hydroquinone cream monotherapy in treating dermal and mixed melasma in an Indian population. This split-face, randomized controlled trial provides critical insights into the short-term benefits and potential complications associated with combination therapy.

## METHODOLOGY

This study was a prospective, comparative, hospital-based, split-face randomized controlled trial conducted at a teaching hospital and tertiary care center in Pune, India, over 18 months (September 2016 to March 2018). The study was approved by the Institutional Ethics Committee and adhered to the principles outlined in the Declaration of Helsinki and its later amendments.

Participants were screened and enrolled based on specific inclusion and exclusion criteria. The inclusion criteria required participants to be adults aged 18 years or older with newly diagnosed dermal or mixed-type melasma as confirmed by Wood's Lamp examination. All participants were required to provide informed consent. Exclusion criteria included pregnancy, lactation, and a history of using other melasma treatments within four weeks before the study. Patients with hypersensitivity to hydroquinone, recent laser treatments, or other systemic conditions contraindicating laser use were also excluded.

A total of 30 patients were recruited for the study. Participants were instructed to apply a broad-spectrum sunscreen with a sun protection factor (SPF) of 30 every morning and to reapply it every 2–3 hours during the study period. Additionally, all participants were advised to apply 2% hydroquinone cream to both sides of the face at night for the study's 10-week duration. Randomization was performed using a simple random sampling technique to assign one side of the face for laser treatment while the contralateral side served as the control.

The experimental side was treated with a low-fluence QS-Nd:YAG laser (1064 nm), using a 6 mm spot size and a fluence of 1.5–1.7 J/cm². Each session consisted of two passes with a 1-week interval between sessions, and four sessions were administered over six weeks. The laser-treated side also received the topical application of 2% hydroquinone cream as described above. The control side was treated with hydroquinone cream alone throughout the study duration.

To assess efficacy, modified Melasma Area and Severity Index (mMASI) scores were recorded at baseline, 6 weeks, and 10 weeks. The mMASI scoring system included assessments of the area of involvement and pigmentation darkness across the forehead, left and right malar regions, and the chin. Photographic documentation was performed using standardized digital clinical photography at each time point. Two independent, blinded dermatologists evaluated the clinical photographs to ensure objective assessment.

Subjective analysis included a patient satisfaction questionnaire using a three-point scale ("satisfied," "somewhat satisfied," and "dissatisfied"). Pain during laser procedures was recorded using a visual analog scale (0–10). Adverse effects such as erythema, post-inflammatory hyperpigmentation, and other complications were documented for both treatment groups.

Statistical analysis was conducted using appropriate tests. Quantitative data were analyzed with unpaired t-tests, while qualitative data were evaluated using Fisher's exact test and Pearson's chi-square test. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using licensed statistical software.

The study's design, incorporating a split-face model and comprehensive evaluation metrics, ensured a robust comparison between the two treatment modalities, providing valuable insights into the efficacy and safety of combination therapy versus monotherapy for melasma in an Indian population.

## RESULTS

A total of 30 patients were enrolled in the study, of whom 22 completed the treatment and follow-up, while eight patients were lost to follow-up before the end of the 10-week study period. The mean age of the participants was 34.73 ± 8.05 years. The majority (40.9%) were aged ≤30 years, 22.7% were between 31–40 years, and 36.4% were over 40 years. Female participants constituted 86.4% of the study population, with a Male:Female ratio of 1:6.3. Among the participants, 50% had pregnancy-induced melasma, while 86.4% reported significant sun exposure as a contributing factor to their condition. Mixed-type melasma was the most common presentation, observed in 68.2% of patients, while 31.8% had dermal-type melasma.

**Table 1: Baseline demographics and clinical characteristics**

| Variable | | Frequency | Percentage |
|---|---|---|---|
| Age | ≤ 30 years | 9 | 40.9 |
| | 31-40 years | 5 | 22.7 |
| | >40 years | 8 | 36.4 |
| Gender | Male n (%) | 3 | 13.6 |
| | Female (n) % | 19 | 86.4 |

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| | | | |
|---|---|---|---|
| Occupation | Housewife | 21 | 70 |
| | Office Job | 3 | 10 |
| | Nursing staff | 6 | 20 |
| | Watchman | 2 | 9.1 |
| | Doctor | 1 | 4.5 |
| | Medical representative | 1 | 4.5 |
| | Student | 1 | 4.5 |
| | Indoor job | 1 | 4.5 |
| Family History | Yes | 1 | 4.5 |
| | No | 21 | 95.5 |
| Pregnancy Induced Melasma | Yes | 11 | 50 |
| | No | 11 | 50 |
| Sun Exposure | Yes | 19 | 86.4 |
| | No | 3 | 13.6 |
| Type of Melasma | Dermal | 7 | 31.8 |
| | Mixed | 15 | 68.2 |
| Laser Treated Side | Left | 16 | 72.7 |
| | Right | 6 | 27.3 |

Patients' subjective perceptions of improvement varied significantly between the laser-treated side and the side treated with hydroquinone cream alone. On the laser-treated side, 63.6% of participants reported improvement, compared to only 31.8% on the hydroquinone-only side. This difference was statistically significant ($p = 0.034$, Chi-square test). However, despite the higher perceived improvement on the laser-treated side, only 31.8% of participants expressed satisfaction with the laser treatment. A significant proportion of participants (59.1%) were dissatisfied with the treatment outcomes, while 9.1% reported being somewhat satisfied. Among the 14 patients who demonstrated improvement on the laser-treated side, eight (36.4%) developed rebound hyperpigmentation, diminishing the overall benefit of combination therapy.


**Fig 1 Improvement on combination treatment side without post inflammatory hyperpigmentation.**

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**Fig 2 Front view showing the difference between laser treated side (left) and topical control side (right)**

Objective assessment using the modified Melasma Area and Severity Index (mMASI) scores revealed significant improvement in pigmentation on both the laser-treated and hydroquinone-only sides over the 10-week study period. On the laser-treated side, the mean mMASI score decreased from 1.36 ± 0.51 at baseline to 0.95 ± 0.45 at 6 weeks ($p = 0.001$) and 1z.02 ± 0.50 at 10 weeks ($p = 0.009$). Similarly, on the hydroquinone-only side, the mean mMASI score decreased from 1.32 ± 0.53 at baseline to 1.20 ± 0.53 at 6 weeks ($p = 0.036$) and 1.04 ± 0.65 at 10 weeks ($p = 0.042$). While both treatments demonstrated statistically significant improvement over time, the differences in mMASI scores between the laser-treated and hydroquinone-only sides at 0, 6, and 10 weeks were not statistically significant ($p > 0.05$, Student's t-test).

The most common complication associated with the laser treatment was transient erythema, which was reported by all participants on the laser-treated side. The erythema resolved spontaneously within 1–2 hours after the procedure. Pain during the laser treatment was reported by 77.3% of participants, with an average score of 4.5 on the visual analog scale. Post-inflammatory hyperpigmentation (PIH) was observed in 36.4% of patients on the laser-treated side, whereas only 9.1% of patients on the hydroquinone-only side experienced similar pigmentation changes. Other complications such as edema or hypopigmentation were not observed in any participant. These findings underscore the need for careful patient counseling regarding the potential for adverse effects with laser-based therapies.

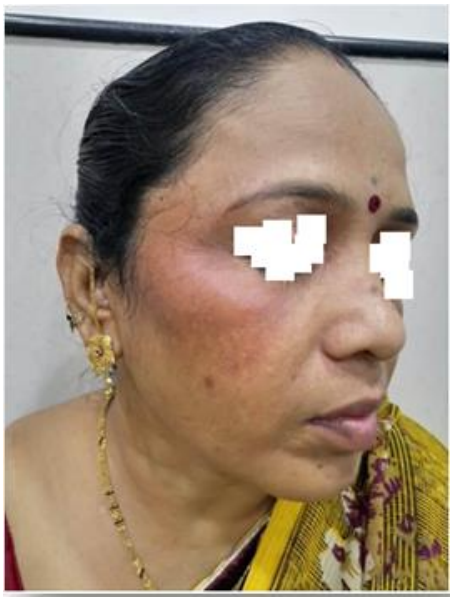

**Fig 3: Erythema after laser treatment which subsided in 1-2 hours.**

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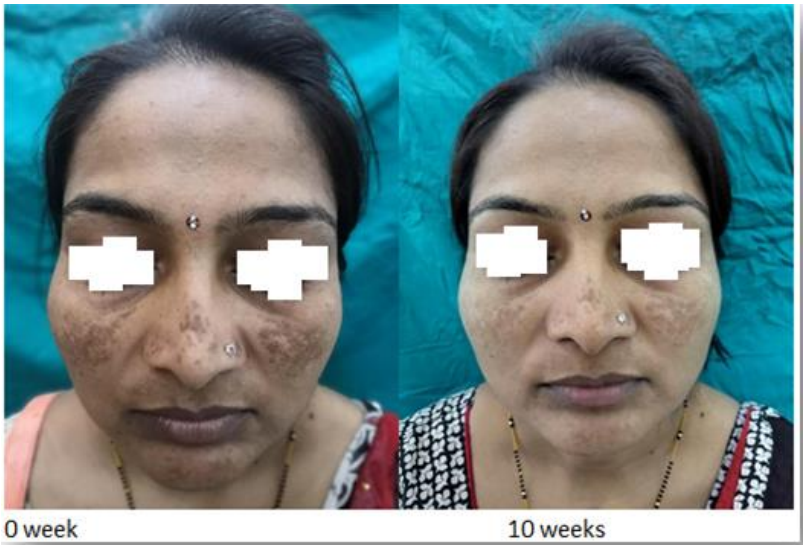


**Fig 4 Both sides Post inflammatory hyper pigmentation observed at 10 weeks**

Photographic documentation supported the clinical *observations*, showing visible improvement in pigmentation on the laser-treated side by week 6. This improvement plateaued by week 10, with several patients developing rebound hyperpigmentation during the follow-up period. The hydroquinone-only side demonstrated a more gradual but consistent reduction in pigmentation, with fewer side effects observed. The differences in pigmentation clearance between the two sides were evident in standardized digital photographs, but the lack of sustained results on the laser-treated side tempered the perceived benefits of combination therapy.

The statistical analysis further validated the study findings. Combination therapy (QS-Nd:YAG laser and 2% hydroquinone cream) showed significantly greater short-term improvement in melasma severity compared to hydroquinone cream alone, as evidenced by Chi-square test results ($p = 0.034$). However, mMASI scores, while improving significantly on both sides over time, did not show a statistically significant difference between the two treatment modalities at any specific time point ($p > 0.05$, Student's t-test).

## DISCUSSION

Melasma is a chronic, relapsing pigmentation disorder that often proves challenging to manage, particularly in individuals with darker skin types. Conventional therapies, including hydroquinone, while effective, have limitations such as slow onset of action, risk of irritation, and high recurrence rates. Low-fluence QS-Nd:YAG laser has gained popularity as an adjunctive treatment for melasma due to its ability to target dermal and epidermal melanin with minimal damage to surrounding tissues. However, as highlighted by recent studies, this modality is not without limitations.

The findings of this study demonstrated that the combination of low-fluence QS-Nd:YAG laser with 2% hydroquinone cream resulted in superior short-term outcomes compared to hydroquinone monotherapy. These results align with those of a systematic review by Lee et al. (2022), which concluded that combination therapies involving low-fluence QS-Nd:YAG laser and topical agents offer better outcomes than monotherapy, albeit with a higher risk of adverse effects.[6]

Similarly, Cervantes et al. (2022) found that low-fluence QS-Nd:YAG laser toning, when combined with topical agents, significantly improved melasma severity scores compared to baseline, although the efficacy diminished over time.[5]

Despite the efficacy of combination therapy, this study found a high incidence of rebound hyperpigmentation and other adverse effects, such as transient erythema and pain during laser treatment. These findings are consistent with the observations of Esmat et al. (2021), who noted that low-fluence QS-Nd:YAG laser is prone to side effects, including post-inflammatory hyperpigmentation (PIH), especially in darker skin types.[4]

The higher prevalence of PIH underscores the importance of cautious application, as excessive fluence or frequent sessions can exacerbate unwanted pigmentation. Abdel Hay et al. (2020) emphasized the role of dermoscopic assessment in monitoring melasma treatments and minimizing the risk of such complications.[7]

While combination therapy showed rapid improvement in pigmentation, its benefits were not sustained, with hyperpigmentation recurring in many patients during follow-up. This aligns with findings by Kwon et al. (2018), who observed a decline in efficacy after cessation of laser treatment and highlighted the need for maintenance therapy to sustain results.[8]

Recent advancements in melasma treatment have explored combining QS-Nd:YAG lasers with other modalities, such as fractional microneedling radiofrequency and oral tranexamic acid, to enhance outcomes and reduce side effects.[9] These alternatives may offer more sustained results and fewer

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complications, suggesting a potential avenue for further research.

## CONCLUSION

The combination of low-fluence QS-Nd:YAG laser and 2% hydroquinone cream demonstrated superior short-term efficacy compared to hydroquinone monotherapy for treating dermal and mixed melasma. However, the therapy was associated with higher rates of adverse effects, including post-inflammatory hyperpigmentation and rebound pigmentation, and its benefits were not sustained beyond the treatment period. Limitations of this study include a small sample size, short follow-up duration, and the absence of comparisons with other emerging treatment modalities. Despite these constraints, the findings highlight the need for cautious patient selection and the importance of maintenance therapy to optimize and sustain outcomes. Future research should focus on long-term effects and comparisons with alternative therapies to refine melasma management strategies.

## REFERENCES

1. McKesey J, Tovar-Garza A, Pandya AG. Melasma treatment: An evidence-based review. Am J Clin Dermatol. 2019;20(3):345–61.
2. Aurangabadkar S. Optimizing Q-switched lasers for melasma and acquired dermal melanoses. J Cutan Aesthet Surg. 2019;12(1):3–9.
3. Guo S, Cai X, Wang S. QPTP is an optimized technology of 1064nm Q-switched Nd:YAG laser for melasma: A pilot study. Lasers Surg Med. 2019;51(4):303–9.
4. Esmat S, Elramly A, Shahin DM, Hilal R. Combining low power fractional CO2 with QS-Nd:YAG toning in the treatment of melasma reduces the incidence of punctate leukoderma. Lasers Surg Med. 2021;53(7):479–85.
5. Cervantes J, Patzelt NM, Al-Janahi S, Kim DH, Chung HJ. Efficacy and safety of low fluence Nd:YAG laser treatment in melasma: A meta-analysis and systematic review. Dermatol Surg. 2022;49(1):36–41.
6. Lee Y, Lee YJ, Lee JM, Han T, Lee J, Choi JE. The low-fluence Q-switched Nd:YAG laser treatment for melasma: A systematic review. Medicina. 2022;58(7):936.
7. Abdel Hay RA, Sayed KS, Mohammed F, Abd El Fattah NA, Ibrahim S. Dermoscopy as a useful tool for evaluating melasma and assessing the response to 1064-nm Q-switched Nd:YAG laser. Dermatol Ther. 2020;33(6):e13629.
8. Kwon H, Choi S, Jung J, Park GH. Combined treatment of melasma involving low-fluence Q-switched Nd:YAG laser and fractional microneedling radiofrequency. J Dermatol Treat. 2018;30(4):352–6.
9. Bandem A, Widianingsih N, Setyaningrum T, Rosita C, Prakoeswa S. Low fluence Q-switched Nd:YAG 1064 nm versus combination with microneedle fractionated radiofrequency for melasma in Indonesian patients. Lasers Med Sci. 2021;36(5):1047–53.
10. Tahir K, Iftikhar U. Low-fluence Q-switched neodymium-doped yttrium aluminum garnet (1064nm) laser for the treatment of facial melasma in local population. J Pak Assoc Dermatol. 2018;27(4):164–8.