AJCM
Avicenna Journal of Clinical Medicine
Avicenna J Clin Med, 2026; 33(1): 13-20 Doi: 10.53208/ajcm.33.1.13
https://sjh.umsha.ac.ir

Original Article

Comparison of Topical 4% Hydroquinone and Topical 2% Glucosamine in the Treatment of Melasma

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Article history:
Received: 16 January 2026
Revised: 15 March 2026
Accepted: 06 May 2026
ePublished: 15 June 2026

BRIEF TEXT

Background and Objective

Melasma is a chronic, relapsing acquired hyperpigmentation disorder characterized by increased melanocyte activity, predominantly affecting sun-exposed areas. It most commonly occurs in women of reproductive age, particularly during the third and fourth decades of life [1, 2, 3, 4]. Pathogenesis of melasma involves biological processes underlying skin color, which results from melanin production by melanocytes in different layers of the skin, a process called melanogenesis.

Melanocytes are specialized cells derived from neural crest that transport melanin-containing melanosomes to adjacent keratinocytes at the dermis-epidermal junction, where melanin is synthesized and stored. The amino acid L-Tyrosine serves as a precursor for melanin biosynthesis and production through various spontaneous enzymatic reactions, also known as the Raper-Mason pathway. The L-Tyrosine increases the production of melanosomes and L-dopachrome by tyrosinase activity [5, 6]. Histopathological findings have revealed increased melanocyte activity, an elevated number of melanophages, and enhanced melanin deposition. In addition, mitochondria, the Golgi apparatus, and endoplasmic reticulum are also increased [7]. Multiple factors have been implicated in the development of melasma, including genetics, ultraviolet radiation, inflammation, oxidative stress, disruption of the skin barrier, estrogens (pregnancy, oral contraceptive pills), acne, and medications [8]. Clinically, melasma presents as bilateral, irregularly bordered hyperpigmented macules or patches affecting the forehead, cheeks, nose, upper lip, and chin. Based on the depth of pigment deposition, it is classified into epidermal, dermal, and mixed types [9]. Clinically, it is also categorized into centrofacial, malar, and mandibular patterns [10]. [11, 12, 13]... [14, 15]. Melasma treatment remains challenging due to its multifactorial etiology, treatment resistance, and high recurrence rate [16].

Topical treatments, including hydroquinone, triple therapy (including hydroquinone, steroid, and tretinoin), azelaic acid, arbutin, vitamin C, tranexamic acid, oligopeptides, silymarin, orchid extract, and herbal extracts, have been used with variable efficacy [1]. Pharmacologic topical agents remain the first-line treatment for induction, maintenance of remission, and prevention of recurrence. However, procedural modalities, such as chemical peels, dermabrasion, and laser therapies (Q-switched Nd-YAG laser, erbium YAG laser, fractional laser, and intense pulsed light), radiofrequency, and microneedling treatments are also used [17]. ... [18-24].

Materials and Methods

This randomized clinical trial was conducted on patients with mild symmetrical facial melasma referred to the dermatology clinic of Hamadan Farshchian Hospital (Sina), Hamadan, Iran, in 2021.

Inclusion criteria were an age range of 18–65 years, presence of mild symmetrical facial melasma, and informed consent. Exclusion criteria comprised other skin diseases, prior facial laser therapy, use of systemic or topical anti-melasma treatments within the past 10 weeks, pregnancy, hypersensitivity to hydroquinone or glucosamine, poor treatment adherence, and failure to use sunscreen regularly.

To control for potential confounding factors, including disease severity, age, and gender, a split-face design was employed. One side of each participant's face was randomly assigned to receive 4% topical hydroquinone, while the contralateral side

received 2% topical glucosamine. Both treatments were applied once nightly for 8 weeks. The participants were followed for two months after completion of therapy. The participants were followed for two months after completion of therapy. Adverse effects were recorded throughout the study period. Clinical evaluation and standardized photographic documentation were performed, and treatment response was assessed using the Modified Melasma Area and Severity Index (MASI) score.

Statistical analysis was performed in SPSS software (version 26). Data were presented as means, standard deviations, frequencies, and percentages. The Shapiro–Wilk test was used to assess normality. Due to non-normal distribution (p<0.05), the Mann–Whitney test was used for between-group comparisons, the Wilcoxon test for within-group comparisons, and Fisher's exact test for adverse event analysis. A p value of less than 0.05 was considered statistically significant.

Results

In total, 24 patients with mild facial melasma were enrolled in this split-face study. One side of the face was treated with 2% topical glucosamine and the contralateral side with 4% topical hydroquinone, resulting in 48 treated facial sides for analysis. The mean age of participants was 36.00±9.83 years (age range: 18-52 years). Regarding gender, the majority of the patients (n=18; 75%) were female. Table 1 summarizes the age groups of the patients.

The mean modified MASI scores before treatment were 4.51 ± 1.70 in the hydroquinone group and 4.50 ± 1.72 in the glucosamine group, which decreased to 1.98 ± 1.11 and 3.15 ± 1.42 after the intervention, respectively (Table 2). The mean reduction values for the hydroquinone and glucosamine groups were 2.54 ± 1.68 and 1.34 ± 1.04, respectively (Figure 1).

Pruritus occurred in two cases (8.3%) in each group, while a burning sensation was reported in one case (4.2%) in the glucosamine group. No statistically significant difference in terms of adverse effects was observed between the two treatment groups.

Discussion

In the present study, 4% topical hydroquinone significantly reduced melasma scores, compared to the pre-treatment state. In a clinical trial performed by Nguyen et al. (2020) in Australia, comparing the effectiveness of 5% cysteamine cream and 4% topical hydroquinone for the treatment of melasma in 20 patients with melasma, hydroquinone resulted in a 2.96-unit (32%) reduction in mMASI score after 16 weeks [25]. In the present study, a reduction of 2.54 units (56.3%) was observed, indicating comparable efficacy.

Findings of the present study are almost consistent with those of a study carried out by Nguyen et al. in terms of the effectiveness of 4% topical hydroquinone in treating melasma. In the present study, 2% topical glucosamine significantly reduced melasma scores, compared to the baseline [26]. … [27]. Therefore, one of the compounds that can be used in the future with retinoids in the treatment of melasma is N-acetylglucosamine [28].

In the present study, the effectiveness of topical hydroquinone 4% in reducing melasma score was significantly higher than that of topical glucosamine 2% [3]. Grimes et al. (2018) also conducted a systematic review of new oral and topical medications for the treatment of melasma. They reported that a combination of 4% hydroquinone with retinoic acid, steroids, and glucosamine is the best combination drug for the treatment of melasma. However, due to potential adverse effects of hydroquinone, such as exogenous ochronosis and depigmentation, alternative agents, such as glucosamine, may be considered in clinical practice [29, 30, 31].

Tirado-Sánchez et al. in their study (2009) compared the effectiveness of dioic acid and hydroquinone for the treatment of melasma. In their study, the frequency of complications in the group receiving hydroquinone 2% included erythema (13%), burning (6%), and itching (20%) [32]. Regarding complications of glucosamine, Lynde et al. in their study (2006) compared a combination of N-acetylglucosamine 2% and niacinamide 4% in the treatment of melasma hyperpigmentation, and reported no adverse effects [33]. Therefore, both hydroquinone and glucosamine can be considered relatively safe drugs with different efficacies for the treatment of melasma hyperpigmentation.

Conclusion

Based on the results, both topical hydroquinone 4% and topical glucosamine 2% were effective and relatively safe for the treatment of mild facial melasma. However, topical hydroquinone 4% demonstrated greater efficacy than topical glucosamine 2%. No

significant difference was observed in the frequency of adverse effects between the two treatments, namely topical hydroquinone 4% and topical glucosamine 2%.

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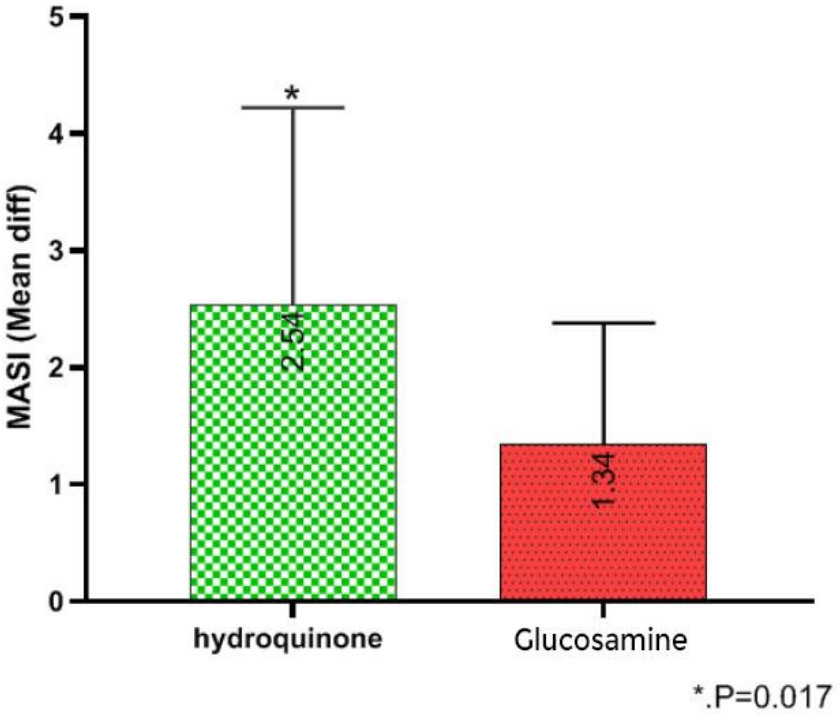
Table 1. Age distribution of patients with melasma participating in the study

Age Group (years)	Frequency	Percentage
Under 30	9	37.5
30–45	9	37.5
Over 45	6	25.0
Total	24	100

Table 2. Mean and standard deviation of modified masi score before and after treatment with topical 4% hydroquinone and 2% glucosamine

Evaluation Time	Hydroquinone (Mean ± SD)	Glucosamine (Mean ± SD)
Before Treatment	4.51 ± 1.70	4.50 ± 1.72
After Treatment	1.98 ± 1.11	3.15 ± 1.42



Extended Abstract

Figure 1. Mean Difference in Modified Melasma Area and Severity Index Score before and after treatment with topical 4% hydroquinone and 2% glucosamine