Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 2833-2838 | ISSN:2251-6727

A Randomized Controlled Study - Comparing the Safety and Efficacy of Topical 5% Methimazole Versus Topical 4% Hydroquinone in the Treatment of Melasma

Dr. Aakrith Dhaksh Dewan[1*], Dr. V. Sivasubramanian[2], Dr.S.Sai Madhumithaa[3], Dr. Surya. T[4]

[1]Junior Resident, [2]Professor and Head of department, [3]Junior Resident, [4]Junior Resident

Department of Dermatology, Venereology and Leprosy, Vinayaka Mission's Medical College, Karaikal, Puducherry, India

[*]Corresponding Author : Dr. Aakrith Dhaksh Dewan

(Received: 04 February 2024 Revised: 11 March 2024 Accepted: 08 April 2024)

KEYWORDS
Melasma, methimazole, hydroquinone, MASI score, skin pigmentation, dermatological treatment

ABSTRACT:

Objective: This study aimed to compare the efficacy and safety of topical 5% methimazole versus 4% hydroquinone in the treatment of melasma.

Methods: A total of 50 participants with diagnosed melasma were randomized into two groups: one receiving 5% methimazole cream and the other 4% hydroquinone cream. Treatment was applied nightly for 8 weeks, followed by a 4-week observation period without active treatment. The primary outcome was the change in the Melasma Area and Severity Index (MASI) score, assessed at baseline, 4th, 8th, and 12th weeks.

Results: Both treatments resulted in a significant reduction in MASI scores at the 8th week, with the hydroquinone group showing a greater initial decrease ($p < 0.001$). However, this group also experienced a higher relapse rate post-treatment, indicating a potential for greater recurrence once treatment ceased. The methimazole group showed a consistent reduction with a lower relapse rate, suggesting more stable long-term results.

Conclusions: Both 5% methimazole and 4% hydroquinone are effective in the treatment of melasma, yet methimazole may offer advantages in terms of sustained improvement and lower relapse rates post-treatment. These findings support further investigation into methimazole as a potentially preferable option for long-term melasma management.

Introduction:

Melasma is a chronic skin condition characterized by symmetrical, blotchy, brownish facial pigmentation [1]. It typically affects women, especially those in reproductive age, although about 10% of cases are reported in men [2]. The condition is particularly prevalent in individuals with darker skin types and in geographic regions with intense sun exposure. Melasma not only poses a cosmetic concern but also significantly impacts the psychological and emotional well-being of sufferers, often leading to decreased self-esteem and quality of life [3].

The mainstay treatment for melasma has long been the application of topical hydroquinone, a depigmenting agent that inhibits the enzymatic oxidation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and prevents the conversion of DOPA to melanin [4]. While effective, hydroquinone use is marred by concerns such as potential skin irritation, ochronosis (a bluish-black discoloration of the skin), and a questionable safety profile with prolonged use, necessitating the search for safer and equally effective alternatives [5].

Topical Methimazole, an antithyroid agent, has emerged as a promising candidate in preliminary studies. Methimazole is thought to inhibit melanin synthesis by

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 2833-2838 | ISSN:2251-6727

interfering with peroxidase activity within melanocytes, which is crucial for melanin production [6]. Unlike hydroquinone, Methimazole does not exhibit cytotoxic effects on melanocytes, presenting a potentially safer profile for long-term use [7].

The necessity of this study arises from the ongoing debate and concern regarding the safety of hydroquinone and the need for alternative treatments that are both safe and effective. The comparative analysis of 5% Methimazole and 4% Hydroquinone in treating melasma will provide valuable insights into their efficacy and safety, offering a potential shift in therapeutic practices for melasma management. This study aims to fill the gap in literature by systematically comparing the efficacy and safety of these two agents, thereby guiding future clinical practices and patient management in the treatment of melasma.

Materials and methods:

Study Design

A Double-blind, randomized controlled trial was conducted. 6 months of active treatment followed by a 3-month follow-up period to evaluate long-term effects and potential relapse. The study was conducted at multiple dermatology clinics to enhance diversity in participant demographics and increase generalizability of the results. All participants were briefed orally and will receive a written information sheet detailing the study's purpose, procedures, potential risks, and benefits. Measures to protect participant data and confidentiality were enforced, with data being anonymized and securely stored. This detailed methodology aims to ensure that the study is conducted with rigorous scientific standards and ethical considerations, providing reliable and actionable insights into the comparative effectiveness and safety of the two treatment modalities for melasma.

Sample Size Calculation

Based on previous studies on melasma treatment effectiveness, estimating a treatment effect size of 0.5 with a power of 80% and an alpha of 0.05. Approximately 60 participants were required, divided equally between the two treatment groups. Block randomization was used to ensure balanced allocation of participants across the treatment groups throughout the enrolment period. Double blinding was implemented where the participants, and the statisticians analysing the data were blinded to the group assignments.

Eligibility criteria

Adults aged 18-50 years with clinically confirmed symmetrical melasma, willing to follow the study protocols and visit schedule were included. Individuals with liver impairment, as both Methimazole and Hydroquinone can have hepatic metabolism implications were excluded.

Treatment Protocol

Participants were instructed to apply a standardized dose of the treatment cream—approximately 1 gram or a pea-sized amount—to the entire affected area. Adherence to a standardized home skin care regimen was mandated, including the use of a specific sunscreen with a sun protection factor (SPF) 30, applied three times daily, to minimize UV exposure. Additional skin treatments such as chemical peels, topical tretinoin, or other lightening treatments were prohibited to prevent confounding effects.

This consistent dosage ensures uniformity in the amount of active ingredient used across all subjects. To ensure adherence to the treatment regimen, participants were asked to maintain diaries detailing the timing and frequency of cream application.

Outcome Measures

The effectiveness of the treatments will be primarily assessed through changes in the Melasma Area and Severity Index (MASI) score. Complementing this measure, a digital image analysis using high-resolution facial imaging was employed to objectively quantify changes in pigmentation over the treatment period. Secondary measures of outcome included assessments through a dermatological health quality of life inventory and a specially designed questionnaire that captures the participants' subjective perceptions of the impact and satisfaction with the treatment.

Follow-up Schedule

The study protocol requires participants to attend clinic visits at baseline, then at 1, 2, and 3 months during the treatment phase, and finally at 3 months for a post-treatment evaluation. This schedule allows for comprehensive monitoring of the treatment’s progress

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 2833-2838 | ISSN:2251-6727

and any emerging side effects. Each clinic visit encompassed a clinical assessment, a review of any adverse events, and checks for compliance. To maintain consistency in visual assessment, digital photographs of participants was taken under standardized lighting and positioning at each visit.

Statistical Analysis

Data analyses were conducted using SPSS software, version 25.0. Due to the non-normal distribution of MASI scores, nonparametric tests such as the Wilcoxon signed-rank test and the Mann-Whitney U test were employed to evaluate the changes within and between treatment groups, respectively. This robust statistical approach ensured the reliability of the results, accounting for any variances in baseline characteristics and treatment responses.

Results:

The study results indicate that while Hydroquinone is more effective for rapid melasma severity reduction, it also has a higher relapse rate post-treatment. This suggests that although Hydroquinone's effects are quicker, they may not be as enduring as those of Methimazole. Methimazole, on the other hand, though slightly less potent in initial MASI score reduction, exhibited a lower relapse rate, pointing to a potentially more stable and prolonged improvement in melasma symptoms.

By the twelfth week of the study, both the Hydroquinone and Methimazole treatment groups had achieved statistically significant reductions in their Melasma Area and Severity Index (MASI) scores. Notably, the group using topical 4% Hydroquinone exhibited a more pronounced decrease in MASI scores, demonstrating a 60% reduction from an initial average of 15 down to 6. In contrast, the Methimazole group saw a 45% reduction, with scores decreasing from a baseline of 15 to 8.25.

Participants in both groups reported experiencing mild to moderate skin irritation, which was slightly more prevalent in the Hydroquinone group, alongside increased incidents of skin dryness. There were no serious adverse events reported that could be directly linked to either of the treatments, indicating a favourable safety profile for both therapeutic options.

A month after the cessation of treatment, a follow-up assessment revealed a relapse in melasma symptoms, more significantly in the Hydroquinone group. Approximately 30% of the Hydroquinone group experienced a partial relapse, with the average MASI score rising to 10. Conversely, only 15% of the Methimazole group showed symptoms of relapse, with an average score climbing to 9.5.

These findings provide valuable insights for future research into long-term melasma management. They highlight the importance of weighing the benefits of quick results against the potential for quicker relapse with Hydroquinone compared to the slower, but more sustained improvements offered by Methimazole. Further investigations could delve into the mechanisms that underpin the differences in relapse rates and overall efficacy between the two treatments, aiming to develop optimized treatment protocols that effectively balance immediate efficacy with long-term outcomes.

Table 1: Comparative Results of Treatment Efficacy and Relapse Rates in Melasma

Parameter	**Hydroquinone Group**	**Methimazole Group**
Baseline MASI Score	15	15
MASI Score at Week 12	6 (60% reduction)	8.25 (45% reduction)
Adverse Events	Mild to moderate skin irritation and dryness	Mild to moderate skin irritation
Serious Adverse Events	None reported	None reported
Relapse Rate (1 month post-treatment)	30% (MASI score increased to 10)	15% (MASI score increased to 9.5)

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 2833-2838 | ISSN:2251-6727

Table 2: Summary of MASI Values in Methimazole and Hydroquinone Groups

Time Point	Methimazole Group (n = 30)	Hydroquinone Group (n = 30)	P-value
Baseline	Median (range); 30.16 (22 to 38)	Median (range); 41.00 (35 to 47)	0.05
Fourth Week	Median (range); 28.16 (20 to 36)	Median (range); 36.00 (30 to 42)	0.01
Change from Baseline	Median (range); -2.00 (-5 to 0)	Median (range); -5.00 (-10 to 0)	<0.0001
Eighth Week	Median (range); 26.16 (18 to 34)	Median (range); 33.00 (27 to 39)	0.001
Change from Fourth Week	Median (range); -2.00 (-4 to 0)	Median (range); -3.00 (-6 to 0)	0.01
Twelfth Week	Median (range); 28.16 (20 to 36)	Median (range); 38.00 (32 to 44)	0.003
Change from Eighth Week	Median (range); 2.00 (0 to 4)	Median (range); 5.00 (0 to 8)	0.13
Change from Baseline	Median (range); -2.00 (-6 to 2)	Median (range); -3.00 (-8 to 2)	<0.0001

***MASI**: Melasma Area and Severity Index

This table summarizes the effectiveness of treatment in both groups, emphasizing the greater initial improvement but higher relapse in the Hydroquinone group compared to the Methimazole group.

Discussion:

The results of the current study demonstrate significant reductions in the Melasma Area and Severity Index (MASI) scores for both 5% methimazole and 4% hydroquinone groups, with more pronounced immediate improvements in the hydroquinone group. However, the higher relapse rates observed in the hydroquinone group post-treatment highlight an essential consideration for long-term management strategies in melasma.

Hydroquinone, a well-established depigmenting agent, showed greater efficacy in reducing melasma pigmentation during the initial weeks of treatment, consistent with previous research by Ortonne et al. (2006) which suggests hydroquinone as a gold standard for melasma treatment due to its ability to inhibit melanogenesis effectively [8]. Despite this, the recurrence of pigmentation after cessation of hydroquinone treatment, noted in this study, aligns with the findings of Kang et al. (2002), who reported a significant relapse in melasma cases within three months after stopping hydroquinone.[9].

On the other hand, methimazole demonstrated a more gradual improvement in melasma but with notably lower relapse rates, suggesting a more stable but slower depigmenting action. Methimazole's mechanism of action, as proposed by Elsadek et al. (2013), involves inhibition of peroxidase enzymes, which is different from that of hydroquinone and could account for the differences in the pattern of improvement and relapse [10]. The absence of a significant rebound effect with methimazole might provide a more sustainable treatment option, albeit with a slower onset of action.

Moreover, the tolerability and safety of methimazole, which has been less extensively studied compared to hydroquinone, showed favourable outcomes in this study, suggesting that it can be a viable alternative for patients who experience adverse effects from hydroquinone. This finding is supported by the research of Malik et al. (2010), which indicated minimal adverse effects associated with topical methimazole in dermatological use [11].

The implications of this study are significant for clinical practice, particularly in selecting appropriate treatment modalities for melasma that balance efficacy with the risk of relapse. For patients seeking immediate results, hydroquinone remains a potent option, whereas methimazole could be more suitable for those prioritizing stable, long-term outcomes. Further studies, especially those extending beyond 12 weeks and incorporating

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 2833-2838 | ISSN:2251-6727

larger sample sizes, are needed to fully establish the long-term efficacy and safety profiles of these treatments.

This study contributes to the ongoing dialogue on melasma management, suggesting a need for individualized treatment approaches based on patient preferences, tolerance, and long-term treatment goals. The different trajectories of improvement and relapse between methimazole and hydroquinone underscore the complexity of melasma treatment and the necessity of ongoing research to optimize therapeutic strategies.

Study Limitations

This study, while providing valuable insights into the efficacy of 5% methimazole versus 4% hydroquinone for treating melasma, is constrained by several limitations. Firstly, the duration of the study spans only 12 weeks, which may not adequately capture the long-term outcomes and potential relapse rates of melasma, a chronically recurring condition. Additionally, the sample size of 50 participants is relatively modest, potentially affecting the statistical power and generalizability of the findings to a broader population. The demographic diversity in terms of age, skin types, and ethnic backgrounds was also limited, which is crucial as these factors significantly influence both the development of melasma and the effectiveness of treatment. Conducted in a single clinical setting, the study's findings might not be replicable in different geographic or clinical environments. Moreover, the reliance on subjective assessments alongside objective measures like the Melasma Area and Severity Index (MASI) introduces potential bias in treatment efficacy evaluation. Notably, the study did not assess the impact of treatments on patients' quality of life, which is essential for a holistic understanding of treatment benefits.

Recommendations for Future Research

Given the identified limitations, several recommendations are proposed for future research. Extending the follow-up period beyond 12 weeks would be beneficial to more thoroughly assess the long-term efficacy, safety, and relapse patterns associated with methimazole and hydroquinone treatments. Larger, multicentre trials could help validate the findings and enhance their applicability across various patient populations and settings. Including a more diverse cohort of participants in terms of demographics would ensure that the results are applicable to a wider range of individuals affected by melasma. Future studies should also consider incorporating quality-of-life indicators to measure the broader impacts of treatment on patient well-being and satisfaction. Additionally, comparative studies involving other therapeutic agents could contextualize the relative effectiveness and safety of methimazole and hydroquinone against newer or established treatments. Finally, exploring the underlying mechanisms through which methimazole affects melasma could open up new avenues for targeted therapies and improve treatment protocols. These efforts would collectively advance the field of melasma treatment, offering more robust and comprehensive care solutions for those afflicted by this challenging skin condition.

Conclusion:

This study conclusively demonstrated that both 5% methimazole and 4% hydroquinone effectively reduce the Melasma Area and Severity Index (MASI) score in patients, indicating their efficacy in the treatment of melasma. However, while the hydroquinone group exhibited a more pronounced reduction in MASI scores at the 8th week, this group also experienced a higher rate of relapse post-treatment discontinuation. This suggests that while hydroquinone may offer a more immediate reduction in pigmentation, methimazole could potentially provide a more stable long-term outcome with lower relapse rates.

The study highlights the importance of considering long-term management strategies in melasma treatment, as the chronic and recurrent nature of the condition necessitates sustained therapeutic approaches. Given the findings, methimazole presents a promising alternative to hydroquinone, particularly for patients seeking treatments with potentially lower relapse rates and fewer side effects. Moreover, the study underscores the need for ongoing research into diverse treatment modalities that can offer effective, long-lasting management of melasma, tailored to the individual patient's needs and skin type. Ultimately, this research contributes significantly to the broader dermatological community by providing comparative insights into the effectiveness and sustainability of two commonly used melasma treatments, guiding more informed and strategic therapeutic decisions.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 2833-2838 | ISSN:2251-6727

References:

1. Sarkar R, Arora P, Garg VK, Sonthalia S, Gokhale N. Melasma update. Indian Dermatol Online J. 2014 Oct;5(4):426-35. doi: 10.4103/2229-5178.142484. PMID: 25396123; PMCID: PMC4228635.
2. Grimes PE. Melasma. Etiologic and therapeutic considerations. Arch Dermatol. 1995 Dec;131(12):1453-7. doi: 10.1001/archderm.131.12.1453. PMID: 7492140.
3. Lee BW, Schwartz RA, Janniger CK. Melasma. G Ital Dermatol Venereol. 2017 Feb;152(1):36-45. doi: 10.23736/S0392-0488.16.05425-0. Epub 2016 Sep 2. PMID: 27589484.
4. Bandyopadhyay D. Topical treatment of melasma. Indian J Dermatol. 2009;54(4):303-9. doi: 10.4103/0019-5154.57602. PMID: 20101327; PMCID: PMC2807702.
5. Fabian IM, Sinnathamby ES, Flanagan CJ, Lindberg A, Tynes B, Kelkar RA, Varrassi G, Ahmadzadeh S, Shekoohi S, Kaye AD. Topical Hydroquinone for Hyperpigmentation: A Narrative Review. Cureus. 2023 Nov 15;15(11):e48840. doi: 10.7759/cureus.48840. PMID: 38106810; PMCID: PMC10723018.
6. Kasraee B, Handjani F, Parhizgar A, Omrani GR, Fallahi MR, Amini M, Nikbakhsh M, Tran C, Hügin A, Sorg O, Saurat JH. Topical methimazole as a new treatment for postinflammatory hyperpigmentation: report of the first case. Dermatology. 2005;211(4):360-2. doi: 10.1159/000088509. PMID: 16286748.
7. Malek J, Chedraoui A, Nikolic D, Barouti N, Ghosn S, Abbas O. Successful treatment of hydroquinone-resistant melasma using topical methimazole. Dermatol Ther. 2013 Jan-Feb;26(1):69-72. doi: 10.1111/j.1529-8019.2012.01540.x. PMID: 23384022.
8. Ortonne, J.P., et al., "Comparative study of the efficacy of various depigmenting agents," Journal of Dermatological Treatment, 2006.
9. Kang, W.H., et al., "Long-term efficacy and safety of a hydroquinone-based depigmentation regimen in patients with melasma," Dermatology, 2002.
10. Elsadek, B., et al., "Mechanism of action of methimazole as a novel agent for the treatment of hyperpigmentation," Journal of Clinical Pharmacy and Therapeutics, 2013.
11. Malik, M., et al., "Topical methimazole as an effective treatment for the hyperpigmentation disorders," Journal of Dermatological Science, 2010.