Comparison of the Use of 5% Methimazole Cream with 4% Kojic Acid in Melasma Treatment

Melazma Tedavisinde %4 Kojik Asit ile %5 Metimazol Krem Kullanımının Karşılaştırılması

Abstract

Objective: This research aims to assess the effectiveness, patient satisfaction, and adverse effects of non-hydroquinone therapy with 5% methimazole cream compared to those using 4% kojic acid in the treatment of melasma.

Methods: A single-blind study of 45 patients with melasma, right-and left-sided treatment was performed by comparing with 5% methimazole cream and night time 4% kojic acid in random order. Sun protection factor 30 sunscreen was used in the morning and afternoon. The evaluation was carried out every 2 weeks by assessing the Melasma Area and Severity Index (MASI), mexameter score, patient satisfaction and adverse effects.

Results: Decreases in MASI score and pigment amount were higher by using 5% methimazole cream than 4% kojic acid. Patient satisfaction, concerning the use of 5% methimazole cream was higher than with 4% kojic acid. Adverse effects were mostly found with the use of 5% methimazole cream.

Conclusion: A comparison of the MASI score, pigment amount and patient satisfaction scales showed that 5% methimazole cream was superior to 4% kojic acid. Five percent methimazole cream can be used as an alternative therapy in the treatment of melasma.

Keywords: Alternative, kojic acid, melasma, Melasma Area and Severity Index, methimazole cream, therapy

Öz

Amaç: Bu araştırma, melazmanın tedavisinde %4’lük kojik asit kullanılanlarla karşılaştırıldığında, hidrokinon olmayan tedavinin, %5’lik metamazol krem ile etkililiğini, hasta memnuniyetini ve yan etkilerini değerlendirerek amaçlamaktadır.

Yöntemler: Melazma tanısı almış 45 hastanın tek kör bir çalışması, sağ ve sol tarafı tedaviyi %5 metamazol kremi ve %4 gece kojik asit ile rastgele sırayla karşılaştırarak yapıldı. Sabah ve öğütteden sonra 30 faktörlü güneş koruyucu kullanıldı. Değerlendirmeye Melazma Alanı ve Şiddet İndeksi (MASI), meksametre skoru, hasta memnuniyeti ve yan etkileri değerlendirilerek 2 haftada bir yapıldı.

Bulgular: MASI skorunda ve pigment miktarındaki azalmalar %5 metamazol kremi kullanılarak kojik asit %4’ten daha yüksek bulunmuştur. %5 metamazol kremi kullanılarak ilgili hasta memnuniyeti %4 kojik asitten daha yüksek. Yan etkiler çoğunlukla metamazol %5 kremlerle daha az olmuştur.

Sonuç: MASI skorunun, pigment miktarının ve hasta memnuniyeti ölçkeleminin karşılaştırılması %5 metamazol kremenin %4 kojik asitten daha üstün olduğunu göstermiştir. Melazma tedavisinde %5 metamazol kremi alternatif tedavi olarak kullanabilir.

Anahtar kelimeler: Alternatif, kojik asit, melazma, Melazma Alanı ve Şiddet İndeksi, metamazol krem, tedavi
Introduction

Melasma is a skin disorder that is difficult to treat using the existing modalities, even when patients have already avoided the risk factors triggering its occurrence (by using sunscreen and avoiding sun exposure) (1). Melasma is a skin lesion-forming cosmetic dermatology condition that affects the patient’s quality of life, both psychosocially and emotionally (2). The current therapies for melasma include sunscreens, depigmenting agents, chemical peels, and the use of lasers. However, to date, there is no substance that is effective in melasma therapy. The ideal treatment should have a strong, fast, and permanent effect, and it should not trigger adverse effects (3,4).

Hydroquinone is a topical therapy accepted by the Food and Drug Administration and is effective as a melasma therapy; however, it has several adverse effects, including contact dermatitis, post-inflammatory hyperpigmentation, leukoderma, and exogenous ochronosis. The latter consists of a skin change to a bluish to blackish state with permanent characteristics (5).

Non-hydroquinone therapy, such as topical retinoids, azelaic acid, kojic acid, arbutin, and mequinol, is widely used for melasma (6). Kojic acid was mentioned in some studies as more suitable than hydroquinone. Kojic acid is considered to have a high sensitizing potential (6,7). Gavin et al. (8) reported the incidence of pigmented contact dermatitis caused by kojic acid. Draelos (9) mentioned a mutagenic effect in cell culture. In addition, some researchers have reported adverse effects of kojic acid use, such as heat and redness, which usually occur early in treatment. Based on research findings concerning the adverse effects of the use of kojic acid, it is still necessary to seek other non-hydroquinone therapies.

One of the relatively recent topical therapies used to treat melasma is 5% thiamazole (methimazole, 1-methyl-2-mercaptopimidazole), a thionamide-class antithyroid drug that works by inhibiting peroxidase in the process of melanogenesis (10). The present research aims to compare the effectiveness, patient satisfaction, and adverse effects of non-hydroquinone therapy with 5% methimazole cream and 4% kojic acid in treating melasma, used as an alternative to hydroquinone use.

Methods

This was a single-blind study comparing left- and right-sided face treatment in a randomized fashion (randomized right-left comparison study). The research was randomized to 45 nurses at Dr. M. Djamil Central Public Hospital, Padang from April 2016 to April 2017. The Committee of the Research Ethics of the Faculty of Medicine, Andalas University, with regards of the protection of human rights and welfare in medical/health research, has carefully reviewed and approved the research protocol of this study with number 034/KEP/FK/2016.

The inclusion criteria were the following: women aged >18 years, suffering from melasma, working indoors from 09.00 to 15.00, and signed an informed consent form. The informed consent stated that the patients have got an explanation and realized the purpose, benefits, and risks which will be happened voluntarily and without being force. Exclusion criteria included pregnancy or lactation, use of hormonal contraceptives for <3 years, a history of hypersensitivity to thiamazole and kojic acid, and a history of topical/systemic melasma treatment (less than 3 months).

At the first visit, review of the patient’s history and basic clinical assessment was conducted by the investigator, including a clinical examination of the degree of melasma based on the Melasma Area and Severity Index (MASI) (light, moderate/severe), Mexameter index examination on both sides of the concern things related to patients’ identity, the duration of melasma, the probable cause of melasma, the site of melasma, frequently used cosmetics, history of previous melasma treatment, family history of melasma, hobbies, contraceptives used, hormone replacement therapy, history of thyroid abnormalities, and use of sunscreen. The examination of melasma lesions included the clinical pattern and light weight of melasma. The melasma clinical pattern was divided into three types (nominal scale): centrophasal type (cheeks, forehead, upper lip/nose, nose, and chin), malar type (cheeks and nose), and mandibular type (mandibular area). The light weight assessment of melasma was conducted by MASI, assessed by location, color/darkness, and homogeneity. The assessed sites were the forehead area (F=forehead), right malar (MR=malar right), left malar (ML=malar left), and chin (C=chin) representing 30%, 30%, 30%, and 10% of the face.

The percentage of total area involvement (A) in each of the four areas was evaluated on a scale of 0-6 (0=no involvement, 1=1%-9%, 2=10%-29%, 3=30%-49%, 4=50%-69%, 5=70%-89%, 6=90%-100%). Darkness (D) of melasma was compared to that of the surrounding normal skin, and homogeneity (H) of hyperpigmentation was measured on a scale of 0-4 (0=none, 1=vague, 2=mild, 3=real, 4=very dark). The MASI score was then calculated for each half of the face using the following equation: 0.15 (DF + HF)-AF + 0.15 (DMR + HMR) AMR + 0.15 (DML + HML) AML + 0.05 (DC + HC) AC. Results were also documented photographically.

Each participant received a 5% methimazole cream (right cheek) and 4% kojic acid (left cheek) and sunscreen. The medicine was applied once daily at night on different faces, while sunscreen was used in the morning and in the afternoon. Participants were asked to note the side effects that arose and were given a control card containing the schedule of the next visit with an interval of 2 weeks between visits. The patient control was performed every 2 weeks during the 12-week study period, by recording the MASI value, the Mexameter index, adverse side effects, and the patient’s satisfaction scale score. Patient global assessment scores, which were an assessment given by patients to their skin disorders, were divided into three categories, namely 0, completely clear, no evidence of hyperpigmentation; 1, only minor visual evidence of hyperpigmentation; and 2, significant evidence of hyperpigmentation.

Methods
At the end of the study, clinical evaluations were conducted, pigment count was examined, and results were documented photographically. At each visit, all adverse effects due to treatment were recorded, namely erythema, itching, burning, or peeling skin.

**Results**

The mean (range) age of patients suffering from melasma was 48.7 (45-64) years, most of whom suffered from the malar pattern with mixed-type melasma (75.5%).

Figure 1 shows that on the first visit (H0), there was no difference between the left and right face MASI scores of 11.7 and 11.9, respectively. From H0 to H4, there was no difference in MASI score on either side of the face. From H4 to H12, there was a slightly greater decrease in the MASI score on the side of the face with 5% methimazole cream compared with kojic acid, showing that the use of 5% methimazole cream gave slightly better results than 4% kojic acid.

Table 1 shows the difference in MASI reduction with the use of 5% methimazole cream and 4% kojic acid. It was found that 5% methimazole cream outperformed 4% kojic acid; however, there was no significant difference between treatments (p=0.299).

Table 2 shows the difference in pigment reduction with the use of 5% methimazole cream and 4% kojic acid; however, it was not statistically significant (p=0.755).

Figure 2 shows patient satisfaction with the use of 5% methimazole cream compared with 4% kojic acid. There was no patient who gave a satisfaction scale score 0, stating “completely clear, no evidence of hyperpigmentation”. The number of patients who gave a satisfaction scale score of 1, stating “there is only minor visual evidence of hyperpigmentation”, was found to be higher with 5% methimazole cream than with 4% kojic acid. Next, the number who gave a satisfaction scale score of 2, stating “significant evidence of hyperpigmentation”, was found to be higher with 4% kojic acid than with 5% methimazole cream.

The following adverse effects were found: nine of the patients treated with 5% methimazole cream experienced redness, burning, and itching. Similarly, adverse effects were also experienced by five patients treated with 4% kojic acid. Adverse effects were felt for longer by those treated with 4% kojic acid cream than by those treated with 5% methimazole cream.

**Discussion**

The use of 5% methimazole cream for melasma therapy has been researched previously. Malek et al. (10) reported a study on the use of 5% methimazole cream on two melasma patients who were hydroquinone resistant. The study was carried out for 8 weeks and found good results: there was a decrease in MASI score, and overall patient satisfaction with therapy was good (10). However, there has been no research reports comparing the use of 5% methimazole cream with other therapies.

The present research showed that after 12 weeks of treatment with 5% methimazole cream and 4% kojic acid, there was little difference in the MASI score, the amount of pigment, the number of patient with 5% methimazole cream and the number of patient with 4% kojic acid

![Figure 1. Diagram of right and left facial Melasma Area and Severity Index changes at each visit](image)

![Figure 2. Comparison of patient global assessment score with the use of 5% methimazole cream and 4% kojic acid after the study](image)

*PGA: Patient global assessment*
and patient satisfaction. This research evaluated the MASI score and the amount of pigment every 2 weeks. Figure 1 shows the ratio of the decrease in the MASI found on the right and left cheeks every 2 weeks during the research. A decrease in the MASI score can be seen on the left and right cheeks. At the end of the study (12 weeks), there was a decrease of 8.0 in the MASI score on the right side of the face 8.6 on the left side of the face. Therefore, the use of 5% methimazole cream gave almost the same result as 4% kojic acid. This corresponds to a change in the amount of pigment ascertained with the Mexameter index, which found no significant difference in the reduction in the amount of pigment between the two treatments (Table 1).

The difference in MASI score reduction and the amount of pigment was not significant because the mechanism of action of both topical drugs affects the process of melanogenesis, in the same way, that is, by inhibiting the activity of tyrosinase. There was little difference in the results because to inhibit the activity of tyrosinase, kojic acid chelates the Cu found associated with the tyrosinase enzyme, so the enzyme becomes inactive (7). Meanwhile, methimazole is an antithyroid drug of the thionamide class that works by inhibiting peroxidase (10,11).

Patient satisfaction scale scores after the study were found to be various in comparison. According to the number of patients reporting a satisfaction scale score of 1, more patients were satisfied with the use of 5% methimazole cream than 4% kojic acid, although the difference was not statistically significant. In contrast, according to those who reported a satisfaction scale score of 2, patients were more satisfied being treated with 4% kojic acid cream than with 5% methimazole cream. At the end of the study, no patients reported a satisfaction scale score of 0 with either of the creams used. These results may be due to different types of melasma suffered by patients, as most of the patients were suffering from mixed-type melasma (epidermal and dermal). Dermal type melasma is less responsive to conventional therapy; therefore, it requires other therapeutic modalities, such as chemical peeling and lasers. In addition, the dermal type requires a longer treatment time, and this study was conducted for only 12 weeks.

The adverse effects found with the use of 5% methimazole cream and 4% kojic acid were almost the same: patients experienced redness, burning sensations, and itching. The adverse effects with the use of 5% methimazole cream were felt especially in the first 2 weeks of the study, subsequently diminished, and then disappeared. With kojic acid cream treatment, these adverse effects were felt for long. The results are consistent with research conducted by Kasraee et al. (11) on the safety of topical methimazole as a melasma therapy. In that study, adverse effects with the use of topical methimazole, characterized by a burning sensation and redness, were reported (11). Malek et al. (10) reported successful topical methimazole treatment in two hydroquinone-resistant melasma patients who also experienced adverse effects, namely a burning sensation and redness. Research by Sardesai et al. (12) investigating 17 melasma patients found side effects of kojic acid in 14% of melasma patients, characterized by redness and a burning sensation. Gajjala et al. (13) also reported adverse effects of kojic acid characterized by redness, a burning sensation, and itching in 26% of melasma patients.

**Study Limitations**

This study’s main limitation is that dermal type melasma is less responsive to conventional therapy; therefore, it requires other therapeutic modalities, such as chemical peeling and lasers. In addition, the dermal type requires a longer treatment time.

**Conclusion**

A comparison of MASI scores, the amount of pigment, and patient satisfaction scales indicated that 5% methimazole cream was superior to 4% kojic acid, although the difference was not statistically significant. In conclusion, 5% methimazole cream can be used as an alternative melasma therapy.

**Ethics**

**Ethics Committee Approval:** The Committee of the Research Ethics of the Faculty of Medicine, Andalas University with regards of the protection of human rights and welfare in medical/health research, has carefully reviewed and approved the research protocol of this study with number 034/KEP/FK/2016.

**Informed Consent:** Written informed consent was obtained from patients/parents of the patients who participated in this study.

**Peer-review:** Internally peer-reviewed.

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**References**


